IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Keiji KUBO, et al.
Serial No.: 11/596,089
Filed: November 9, 2006
For: CYCLIC AMIDE DERIVATIVE, AND ITS PRODUCTION AND USE

Group Art Unit: 1625
Examiner: CHANG, CELIA C.

VERIFICATION OF ENGLISH TRANSLATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Tadayuki MOTOYAMA, declare that I am conversant in both the Japanese and English languages and that the English translation as attached hereto is an accurate translation of WO 2004/035579 A1 published on April 29, 2004.

Signed this 27th day of August, 2009.

Tadayuki Motoyama

Tadayuki MOTOYAMA

DESCRIPTION

IMIDAZOPYRIDINE DERIVATIVE, PROCESS FOR PRODUCING THE SAME, AND USE

Technical Field

The present invention relates to a novel imidazopyridine derivative which inhibits activated blood coagulation factor X (FXa) to exhibit anticoagulant activity and antithrombotic activity, and therefore is useful for preventing and treating arterial and venous thrombotic obstructive diseases, inflammation, cancer and the like; and a process for producing the same and use.

Background Art

It is important to suppress the formation of thrombus for preventing and treating myocardial infarction, cerebral thrombosis and the like, and various antithrombin agents, platelet aggregation inhibitors and the like have been studied and developed as thrombosis inhibitors. However, since not only platelet aggregation inhibitors, but also anti-thrombin agents suppress the aggregation of platelets in addition to their anticoagulant activity, these medicaments tend to cause bleeding and the like as adverse side effects. Therefore, there is a problem in their safety. On the other hand, it is considered that the FXa

inhibitor is a safe anticoagulant agent for specifically inhibiting only a coagulating factor.

Hitherto, compounds having the FXa inhibiting activity have been disclosed, for example, in the following publications. JP 7-112970 A, JP 5-208946 A, WO 96/16940, WO 96/40679, WO 96/10022, WO 97/21437, WO 99/26919, WO 99/33805, WO 00/09480, WO 01/44172, WO 02/06234, US 2002/0045616 A, and Journal of Medicinal Chemistry, 1998, Vol. 41, p.3357.

Object of the Invention

Development of a novel compound is desired, which has excellent efficacy, oral absorbability, sustained effect and the like, with fewer side effects, and which is more useful as a therapeutic agent for thrombosis, as compared with conventional FXa inhibitors.

Disclosure of Invention

The inventors of the present invention envisaged that an imidazopyridine derivative having high selectivity for and strong inhibiting action against FXa can exhibit a sustained and sufficient effect upon oral administration, and thus would be useful for prevention and treatment of thrombotic occlusive diseases in arteries and veins, inflammation, cancer and the like. Thus, they have

devotedly continued their study.

As a result, the inventors have found that a novel imidazopyridine derivative represented by the following the formula (I), or a salt thereof (hereinafter, may be referred to as a compound (I)) has a selectively strong FXa inhibiting effect and excellent safety, and thus exhibits a sustained and sufficient effect upon oral administration, thereby completing the present invention.

That is, the present invention relates to:

(1) A compound represented by the formula (I):

(I)

wherein Ar represents an optionally substituted naphthyl group, an optionally substituted phenyl group, an optionally substituted indolyl group, or an optionally substituted benzothienyl group; X represents an optionally substituted divalent hydrocarbon group; Z represents -CO-, -SO-, or $-SO_2-$; ring A represents an optionally substituted piperazine ring or an optionally substituted homopiperazine ring; ring B represents an optionally substituted imidazopyridine ring; and a represents 0, 1 or 2; or a salt theereof;

(2) A prodrug of the compound according to the above-mentioned (1);

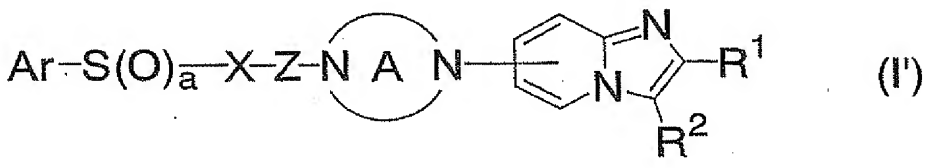
(3) The compound according to the above-mentioned (1),

wherein ring B is an optionally substituted imidazo[1,2-a]pyridine ring;

(4) The compound according to the above-mentioned (1), wherein ring B is an imidazo[1,2-a]pyridine ring which may be substituted with one or more substituents selected from a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted amino group, a nitro group and an optionally esterified or amidated carboxyl group;

(5) The compound according to the above-mentioned (1), wherein ring B is an imidazo[1,2-a]pyridine ring which may be substituted with an optionally substituted C_{1-4} alkyl group;

(6) The compound according to the above-mentioned (1), wherein the formula (I) is the formula (I')



(I')

wherein R^1 and R^2 each independently represent a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon atom, an optionally substituted amino group, a nitro group, or an optionally esterified or amidated carboxyl group; and other symbols have the same meanings as defined in the above-mentioned (1);

(7) The compound according to the above-mentioned (6), wherein R^1 and R^2 are each independently a hydrogen atom,

or an optionally substituted C_{1-4} alkyl group;

(8) The compound according to the above-mentioned (1), wherein X is an optionally substituted divalent chain hydrocarbon group;

(9) The compound according to the above-mentioned (1), wherein X is an optionally substituted C_{1-8} alkylene group;

(10) The compound according to the above-mentioned (1), wherein Z is -CO-;

(11) The compound according to the above-mentioned (1), wherein ring A is an optionally substituted piperazine ring;

(12) The compound according to the above-mentioned (1), wherein a is 2;

(13) The compound according to the above-mentioned (6), wherein Ar is a naphthyl group substituted with a halogen atom, or a indolyl group substituted with a halogen atom; X is a C_{1-8} alkylene group; Z is -CO-; R^1 and R^2 are each independently a hydrogen atom, a C_{1-4} alkyl group which may be substituted with a hydroxyl group, or an esterified carboxyl group; and a is 2;

(14) A compound selected from the group consisting of 5-[4-[3-[(5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl-2-methylimidazo[1,2-a]pyridine, 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine, 5-[4-[3-[(6-chloro-2-

naphthyl)sulfonyl]propionyl]-3-(methylaminocarbonyl)methyl-1-piperazinyl]2-methylimidazo[1,2-a]pyridine, 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-aminocarbonyl-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine and 1-[3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl]-4-[2-(2-hydroxyethyl)imidazo[1,2-a]pyridin-5-yl]-2-piperazinecarboxamide, or a salt thereof or a prodrug thereof;

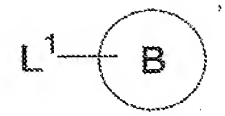
(15) A pharmaceutical comprising the compound according to the above-mentioned (1) or (2);

(16) The pharmaceutical according to the above-mentioned (15), which is an anticoagulant;

(17) The pharmaceutical according to the above-mentioned (15), which is an activated blood coagulation factor X inhibitor;

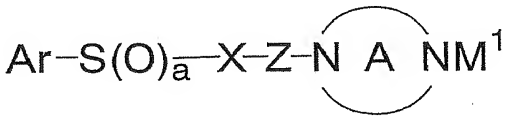
(18) The pharmaceutical according to the above-mentioned (15), which is a medicament for preventing or treating myocardial infarction, cerebral infarction, deep vein thrombosis, pulmonary thromboembolism, atherosclerotic obliterans, economy-class syndrome, or thromboembolism during and post operation;

(19) A process for producing the compound according to the above-mentioned (1), which comprises reacting a compound represented by the formula (II):



(II)

wherein L^1 represents a leaving group, and the other symbols have the same meanings as defined in the above-mentioned (1), or a salt thereof, with a compound represented by the formula (III):

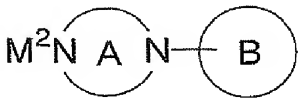


(III)

wherein M^1 represents a hydrogen atom, an alkali metal, an alkali earth metal or a leaving group, and the other symbols have the same meanings as defined in the above-mentioned (1), or a salt thereof; or reacting a compound represented by the formula (IV):

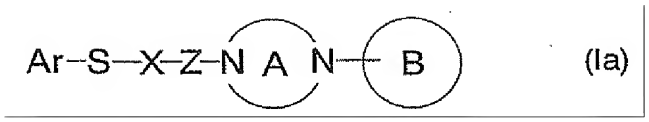
Ar-S(O)a-X-Z-L^2 (IV)

wherein L^2 represents a leaving group, and the other symbols have the same meanings as defined in the above-mentioned (1), or a salt thereof, with a compound represented by the formula (V):



(V)

wherein M^2 represents a hydrogen atom, an alkali metal, an alkali earth metal or a leaving group, and the other symbols have the same meanings as defined in the above-mentioned (1), or a salt thereof; or reacting a compound represented by the formula (Ia):



(Ia)

wherein symbols have the same meanings as defined in the above-mentioned (1), or a salt thereof, with an oxidizing agent; or reacting a compound represented by the formula (VI):

$Ar\text{-}S(O)a\text{-}M^3$ (VI)

wherein M^3 represents a hydrogen atom, a hydroxyl group, an alkali metal, an alkali earth metal or a leaving group, and the other symbols have the same meanings as defined in the above-mentioned (1), or a salt thereof, with a compound represented by the formula (VII):

(VII)

wherein X' represents an alkenyl group, an alkynyl group, or an alkyl group having a leaving group, and the other symbols have the same meanings as defined in the above-mentioned (1), or a salt thereof; and optionally subjecting the compound obtained by the above reaction to hydrolysis, esterification, amidation, alkylation, acylation, reduction, oxidation or/and deprotection reaction;

(20) 3-(5-Halogeno-2-indolyl)sulfonylpropionic acid, an ester thereof or an amide thereof, or 3-(1-tert-butoxycarbonyl-5-halogeno-2-indolyl)sulfonylpropionic acid, an ester thereof or an amide thereof, or a salt thereof;

(21) A method for inhibiting blood coagulation in a mammal, which comprises administering an effective amount of the compound according to the above-mentioned (1) or a salt thereof, or a prodrug thereof to the mammal;

(22) A method for inhibiting an activated blood coagulation factor X in a mammal, which comprises administering an effective amount of the compound according to the above-mentioned (1) or a salt thereof, or a prodrug thereof to the mammal;

(23) A method for preventing or treating myocardial infarction, cerebral infarction, deep vein thrombosis, pulmonary thromboembolism, atherosclerotic obliterans, economy-class syndrome, or thromboembolism during and post operation in a mammal, which comprises administering an effective amount of the compound according to the above-mentioned (1) or a salt thereof, or a prodrug thereof to the mammal;

(24) Use of the compound according to the above-mentioned (1) or a salt thereof, or a prodrug thereof, for manufacturing a medicament for inhibiting blood coagulation;

(25) Use of the compound according to the above-mentioned (1) or a salt thereof, or a prodrug thereof, for manufacturing a medicament for inhibiting an activated blood coagulation factor X;

(26) Use of the compound according to the above-mentioned (1) or a salt thereof, or a prodrug thereof, for manufacturing a medicament for preventing or treating myocardial infarction, cerebral infarction, deep vein thrombosis, pulmonary thromboembolism, atherosclerotic obliterans, economy-class syndrome, or thromboembolism during and post operation; and the like.

In the above formulas, Ar represents an optionally substituted naphthyl group, an optionally substituted phenyl group, an optionally substituted indolyl group, or an optionally substituted benzothienyl group.

Here, examples of the "naphthyl group" include 1-naphthyl and 2-naphthyl. Among these, 2-naphthyl is preferred. Examples of the "indolyl group" include 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl and the like. Among these, 2-indolyl and the like is preferred. Examples of the "benzothienyl group" include 2-benzothienyl, 3-benzothienyl, 4-benzothienyl, 5-benzothienyl, 6-benzothienyl, 7-benzothienyl and the like. Among these, 2-benzothienyl and the like is preferred.

Examples of the substituent which may be carried by the "optionally substituted naphthyl group, the "optionally substituted phenyl group", the "optionally substituted

indolyl group" and the "optionally substituted benzothienyl group" represented by Ar include an optionally substituted alkyl group, an optionally substituted alkenyl group, an optionally substituted alkynyl group, an optionally substituted aryl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkenyl group, an optionally substituted amino group, an optionally substituted imidoyl group [for example, a group represented by the formula: -C(U')=N-U, wherein U and U' are each a hydrogen atom or a substituent (U is preferably a hydrogen atom), etc.], an optionally substituted amidino group [for example, a group represented by the formula: -C(NT'T")=N-T, wherein T, T' and T" are each a hydrogen atom or a substituent (T is preferably a hydrogen atom), etc.], an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally esterified or amidated carboxyl group, an optionally substituted thiocarbamoyl group, an optionally substituted sulfamoyl, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc., preferably chlorine, bromine, etc.), a cyano group, a nitro group, an acyl group (carboxylic acid-derived acyl group, sulfonic acid-derived acyl group, sulfinic acid-derived acyl group), and the like. Any of these substituents may be substituted at 1 to 5 (preferably, 1 to 3) substitutable positions.

The aryl group in the "optionally substituted aryl group" includes, for example, C_{6-14} aryl such as phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl. Here, examples of the substituent which may be carried by the aryl group include a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a lower alkyl group (e.g., C_{1-6} alkyl such as methyl, ethyl and propyl), a lower alkenyl group (e.g., C_{2-6} alkenyl such as vinyl and allyl), a lower alkynyl group (e.g., C_{2-6} alkynyl such as ethynyl and propargyl), an aryl group (e.g., C_{6-14} aryl such as phenyl and naphthyl), a lower alkoxy group (e.g., C_{1-6} alkoxy such as methoxy, ethoxy and propoxy), a lower alkylthio group (e.g., C_{1-6} alkylthio such as methylthio, ethylthio and propylthio), an optionally substituted amino group, an optionally substituted hydroxyl group, a cyano group, a nitro group, a nitroso group, an optionally substituted amidino group, an optionally substituted imidoyl group, an acyl group (e.g., C_{1-6} alkanoyl such as formyl, acetyl, propionyl and pivaloyl, benzoyl, etc.), a carboxyl group, a lower alkoxycarbonyl group (e.g., C_{1-6} alkoxycarbonyl such as methoxycarbonyl and ethoxycarbonyl), an optionally substituted carbamoyl group (e.g., a carbamoyl group which may be substituted with C_{1-6} alkyl or acyl (e.g., formyl, C_{2-6} alkanoyl, benzoyl, optionally halogenated C_{1-6} alkoxycarbonyl, optionally halogenated C_{1-6} alkylsulfonyl,

benzenesulfonyl, etc.) which may be substituted with a 5- to 6-membered aromatic monocyclic heterocyclic group (e.g., pyridinyl, etc.), 1-azetidinylcarbonyl, 1-pyrrolidinylcarbonyl, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl (the sulfur atom may be oxidized), 1-piperazinylcarbonyl, etc.) and the like. Any of these substituents may be substituted at 1 to 3 substitutable positions.

The "optionally substituted amino group", the "optionally substituted hydroxyl group" and the "optionally substituted amidino" as the substituents which may be carried by the aryl group in the "optionally substituted aryl group", mention may be made of the same group groups as the "optionally substituted amino group", the "optionally substituted hydroxyl group" and the "optionally substituted amidino" as the substituents which may be carried by the "optionally substituted naphthyl group", the "optionally substituted phenyl group", the "optionally substituted indolyl group" and the "optionally substituted benzothienyl group" represented by Ar described below.

The cycloalkyl group in the "optionally substituted cycloalkyl group" as a substituent includes, for example, C_{3-7} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Here, as the substituent for the cycloalkyl group, mention may be made of the same

groups of the same number as the substituents in the "optionally substituted aryl group", and an oxo group, a thioxo group and the like.

The cycloalkenyl group in the "optionally substituted cycloalkenyl group" as a substituent includes, for example, C_{3-6} cycloalkenyl such as cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl. Here, as the substituent for the optionally substituted cycloalkenyl group, mention may be made of the same groups of the same number as the substituents in the "optionally substituted aryl group", and an oxo group, a thioxo group or the like.

The alkyl group in the "optionally substituted alkyl group" as a substituent includes, for example, C_{1-6} alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, 1-methylpropyl, n-hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl and 2,2-dimethylpropyl. Here, as the substituent for the alkyl group, mention may be made of the same groups of the same number as the substituents in the "optionally substituted aryl group", and an oxo group, a thioxo group, and the like

The alkenyl group in the "optionally substituted alkenyl group" as a substituent includes, for example, C_{2-6} alkenyl such as vinyl, allyl, isopropenyl, 2-methylallyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-

butenyl, 2-ethyl-1-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl. Here, as the substituent for the alkenyl group, mention may be made of the same groups of the same number as the substituents in the "optionally substituted aryl group", and an oxo group, a thioxo group and the like.

The alkynyl group of the "optionally substituted alkynyl group" as a substituent includes, for example, C_{2-6} alkynyl such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl. Here, as the substituent for the alkynyl group, mention may be made of the same groups of the same number as the substituents in the "optionally substituted aryl group", and an oxo group, a thioxo group, and the like.

The heterocyclic group in the "optionally substituted heterocyclic group" as a substituent includes, for example, an aromatic heterocyclic group, a saturated or unsaturated non-aromatic heterocyclic group (aliphatic heterocyclic group) or the like, respectively containing at least one (preferably one to four, and more preferably one to two) heteroatom of one to three kinds (preferably one to two klinds) selected from oxygen, sulfur and nitrogen atoms and

the like, as an atom constituting the ring system (ring atom).

Examples of the "aromatic heterocyclic group" include a 5- to 6-membered aromatic monocyclic heterocyclic group such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and a 8- to 16-membered (preferably, 8- to 12-membered) aromatic fused heterocyclic group (preferably, a heterocyclic group derived from a heterocycle resulting from condensation of one to two (preferably, one) heterocycles constituting the 5- to 6-membered aromatic monocyclic heterocyclic group, with one to two benzene rings (preferably, one), or a heterocyclic group derived from a heterocycle resulting from condensation of two to three (preferably, two) identical or different heterocycles constituting the 5- to 6-membered aromatic monocyclic heterocyclic group, such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl,

quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, buteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[l,2-a]pyridyl, imidazo[l,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, and 1,2,4-triazolo[4,3-b]pyridazinyl.

Examples of the "non-aromatic heterocyclic group" include a 3- to 8-membered (preferably, 5- to 6-membered) saturated or unsaturated (preferably, saturated) non-aromatic monocyclic heterocyclic group (aliphatic monocyclic heterocyclic group) such as oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, and piperazinyl; a heterocyclic group derived from a heterocycle resulting from condensation of one to two (preferably, one) heterocycles which constitute the non-aromatic monocyclic heterocyclic group such as 1,3-dihydroisoindolyl, with one to two (preferably, one) benzene rings; a heterocyclic group derived from a heterocycle resulting from condensation of one to two (preferably, one) heterocycles constituting the non-aromatic monocyclic heterocyclic group, with one to two

(preferably, one) heterocycles constituting the 5- to 6-membered aromatic monocyclic heterocyclic group; or a non-aromatic heterocyclic group resulting from saturation of part or all of the double bonds in the aromatic monocyclic heterocyclic group or aromatic fused heterocyclic group, such as 1,2,3,4-tetrahydroquinolyl and 1,2,3,4-tetrahydroisoquinolyl.

The substituent which may be carried by the heterocyclic group in the "optionally substituted heterocyclic group" includes, for example, the same groups of the same number as the substituents in the "optionally substituted aryl group".

The substituent in the "optionally substituted amino group", "optionally substituted imidoyl group", "optionally substituted amidino group", "optionally substituted hydroxyl group" and "optionally substituted thiol group" as substituents which may be carried by a naphthyl group, a phenyl group, an indolyl group and a thienyl group of the "optionally substituted naphthyl group", "optionally substituted phenyl group", "optionally substituted indolyl group" and "optionally substituted benzothienyl group" represented by Ar, mention may be made of, for example, a lower alkyl group (e.g., C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl) which may be substituted with a substituent selected

from a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.) and an optionally halogenated C_{1-6} alkoxy group (e.g., methoxy, ethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, trichloromethoxy, 2,2,2-trichloroethoxy, etc.), an acyl group (C_{1-6} alkanoyl (e.g., formyl, acetyl, propionyl, pivaloyl, etc.), benzoyl, a C_{1-6} alkylsulfonyl group (e.g., methanesulfonyl, etc.), benzenesulfonyl, etc.), an optionally halogenated C_{1-6} alkoxycarbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, trifluoromethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, trichloromethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.), a C_{1-6} alkoxycarbonyl group which may be substituted with phenyl (e.g., benzyloxycarbonyl, etc.), a heterocyclic group (the same groups as the "heterocyclic groups" of the "optionally substituted heterocyclic group") and the like. The "amino group" of the "optionally substituted amino group" as a substituent may be substituted with an optionally substituted imidoyl group (e.g., C_{1-6} alkylimidoyl (e.g., formylimidoyl, acetylimidoyl, etc.), C_{1-6} alkoxyimidoyl, C_{1-6} alkylthioimidoyl, amidino, etc.), an amino group which may be substituted with one to two C_{1-6} alkyl, or the like, and two substituents together with a nitrogen atom may form a cyclic amino group in some cases. In this case, examples of the cyclic amino group include a 3- to 8-membered (preferably, 5- to 6-membered) cyclic amino group such as

1-azetidinyl, 1-pyrrolidinyl, piperidino, thiomorpholino, morpholino, 1-piperazinyl and 1-piperazinyl which may have a lower alkyl group (e.g., a C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl and hexyl), an aralkyl group (e.g., a C_{7-10} aralkyl group such as benzyl and phenethyl), an aryl group (e.g., a C_{6-10} aryl group such as phenyl, 1-naphthyl and 2-naphthyl) or the like on the 4-position, 1-pyrrolyl, 1-imidazolyl, or the like.

Examples of the "optionally esterified or amidated carboxyl" as a substituent include free carboxyl, esterified carboxyl, amidated carboxyl and the like.

Examples of the "esterified carboxyl" include a lower alkoxycarbonyl group, an aryloxycarbonyl group, an aralkyloxycarbonyl group and the like.

Examples of the "lower alkoxycarbonyl group" include C_{1-6} alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl and neopentyloxycarbonyl and the like. Among them, C_{1-3} alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl is preferred.

The "aryloxycarbonyl group" is preferably, for example, C_{7-12} aryloxycarbonyl such as phenoxycarbonyl, 1-naphthoxycarbonyl and 2-naphthoxycarbonyl.

The "aralkyloxycarbonyl group" is preferably, for example, C_{7-10} aralkyloxycarbonyl such as benzyloxycarbonyl or phenethyloxycarbonyl (preferably, C_{6-10} aryl-C_{1-4} alkoxycarbonyl, etc.) or the like.

The "aryloxycarbonyl group" and "aralkyloxycarbonyl group" may be substituted, and as the substituent, the same groups of the same number as the groups exemplified as the substituents for the aryl group and aralkyl group as the exemplary substituents for the N-monosubstituted carbamoyl group are used.

The "amidated carboxyl" may be exemplified by N-monosubstituted carbamoyl and N,N-disubstituted carbamoyl, in addition to unsubstituted carbamoyl.

The substituent for the "N-monosubstituted carbamoyl" includes, for example, a lower alkyl group (e.g., C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl), a lower alkenyl group (e.g., C_{2-6} alkenyl such as vinyl, allyl, isopropenyl, propenyl, butenyl, pentenyl and hexenyl), a cycloalkyl group (e.g., C_{3-6} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), an aryl group (e.g., C_{6-10} aryl such as phenyl, 1-naphthyl and 2-naphthyl), an aralkyl group (e.g., C_{7-10} aralkyl such as benzyl and phenethyl, preferably phenyl-C_{1-4} alkyl, etc.), an arylalkenyl group (e.g., C_{8-10} arylalkenyl such as cinnamyl, preferably phenyl-C_{2-4} alkenyl,

etc.), a heterocyclic group (for example, the same group as the "heterocyclic group" in the "optionally substituted heterocyclic group"), an amino which may be substituted with one to two C_{1-6} alkyl groups (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, etc.) or the like. The lower alkyl group, lower alkenyl group, cycloalkyl group, aryl group, aralkyl group, arylalkenyl group and heterocyclic group may be substituted, and examples of the substituent include a hydroxyl group, an optionally substituted amino group [this amino group may be substituted with one or two substituents such as a lower alkyl group (e.g., C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl), an acyl group (e.g., C_{1-6} alkanoyl such as formyl, acetyl, propionyl and pivaloyl, benzoyl, etc.), carboxyl, a C_{1-6} alkoxycarbonyl group and the like], a halogen atom (for example, fluorine, chlorine, bromine, iodine, etc.), a nitro group, a cyano group, a lower alkyl group which may be substituted with one to five halogen atoms (for example, fluorine, chlorine, bromine, iodine, etc.), a lower alkoxy group which may be substituted with one to five halogen atoms (for example, fluorine, chlorine, bromine, iodine, etc.) and the like. Examples of the lower alkyl group include a C_{1-6} alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl

and hexyl, and the like, and particularly methyl, ethyl and the like are preferred. Examples of the lower alkoxy group include a C_{1-6} alkoxy group such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy, and the like, and particularly methoxy, ethoxy and the like are preferred. It is preferable that these substituents are the same or substituted with one, two or three (preferably, one or two) substituents.

The "N,N-disubstituted carbamoyl group" refers to a carbamoyl group having two substituents on the nitrogen atom, and examples of the substituent include, on one side, the same groups as the substituents in the "N-monosubstituted carbamoyl group", and on the other side, for example, a lower alkyl group (e.g., C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl and hexyl), a C_{3-6} cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), a C_{7-10} aralkyl group (e.g., benzyl, phenethyl, etc., preferably phenyl-C_{1-4} alkyl, etc.) and the like. Further, two substituents together with the nitrogen atom may form cyclic amino in some cases, and in this case, the cyclic aminocarbamoyl group includes, for example, a 3- to 8-membered (preferably, 5- to 6-membered) cyclic aminocarbonyl group such as 1-azetidinylcarbonyl, 1-pyrrolidinylcarbonyl, piperidinocarbonyl, morpholinocarbonyl,

thiomorpholinocarbonyl (the sulfur atom may be oxidized), 1-piperazinylcarbonyl, and 1-piperazinylcarbonyl which may have a lower alkyl group (e.g., C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl and hexyl), an aralkyl group (e.g., C_{7-10} aralkyl such as benzyl, phenethyl, etc.), an aryl group (e.g., C_{6-10} aryl such as phenyl, 1-naphthyl and 2-naphthyl) or the like on the 4-position.

As the substituent for the "optionally substituted thiocarbamoyl group" and "optionally substituted sulfamoyl group", mention may be made of the same groups as the substituents for the "optionally substituted carbamoyl" or the like.

The "acyl group" as a substituent includes, for example, a carboxylic acid-derived acyl group, a sulfonic acid-derived acyl group, a sulfinic acid-derived acyl group or the like.

The "carboxylic acid-derived acyl" includes, for example, groups formed by the binding of carbonyl with a hydrogen atom or a substituent having the "N-monosubstituted carbamoyl group" on the nitrogen atom. Preferably, mention may be made of C_{1-6} alkanoyl such as formyl, acetyl, propionyl and pivaloyl, benzoyl or the like.

The "sulfonic acid-derived acyl" includes, for example, groups formed by the binding of sulfonyl with one

substituent having the "N-monosubstituted carbamoyl group" on the nitrogen atom. Preferably, mention may be made of C_{1-6} alkylsulfonyl such as methanesulfonyl and ethanesulfonyl, benzenesulfonyl and toluenesulfonyl.

The "sulfinic acid-derived acyl" includes, for example, groups formed by the binding of sulfinyl with a substituent having the "N-monosubstituted carbamoyl group" on the nitrogen atom. Preferably, mention may be made of C_{1-6} alkylsulfonyl such as methanesulfinyl and ethanesulfinyl, or the like.

Ar is preferably naphthyl which may be substituted with one or more substituents selected from a halogen atom, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, optionally substituted amino, nitro, cyano, optionally substituted amidino, and optionally esterified or amidated carboxyl; or indolyl which may be substituted with one or more substituents selected from a halogen atom, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, optionally substituted amino, nitro, cyano, optionally substituted amidino, and optionally esterified or amidated carboxyl.

Among these, Ar is preferably optionally substituted naphthyl, and inter alia, naphthyl (preferably, 2-naphthyl, etc.) is preferred.

Particularly, Ar is preferably naphthyl substituted with a halogen atom.

In the formulas, X is an optionally substituted divalent chain hydrocarbon group.

The "optionally substituted divalent hydrocarbon group" represented by X includes, for example, an "optionally substituted divalent chain hydrocarbon group", an "optionally substituted divalent cyclic hydrocarbon group" or the like.

Examples of the "divalent chain hydrocarbon group" of the "optionally substituted divalent chain hydrocarbon group" represented by X include C_{1-8} alkylene such as methylene, ethylene, trimethylene and tetramethylene, C_{2-8} alkenylene such as vinylene, propylene, 1- or 2-butenylene and butadienylene, C_{2-8} alkynylene such as ethynylene, 1- or 2-propynylene and 1- or 2-butynylene.

The "divalent cyclic hydrocarbon group" in the "optionally substituted divalent cyclic hydrocarbon group" represented by X includes, for example, a group formed by eliminating any one hydrogen atom from the cycloalkyl group, cycloalkenyl group, aryl group, or the like. Among these, a divalent aryl group, particularly phenylene (1,2-phenylene, 1,3-phenylene, 1,4-phenylene) is preferred.

The "optionally substituted divalent chain hydrocarbon group" represented by X is preferably an optionally substituted divalent cyclic hydrocarbon group, and among these, preferred is an optionally substituted C_{1-6} alkylene

group.

The substituent which may be carried by the "divalent hydrocarbon group" in the "optionally substituted divalent hydrocarbon group" represented by X includes, for example, the same groups as the substituents which may be carried by the "optionally substituted naphthyl group", "optionally substituted phenyl group", "optionally substituted indolyl group" and "optionally substituted benzothienyl group" represented by Ar, an oxo group, or the like. Among these, a lower alkyl group (e.g., C_{1-6} alkyl such as methyl, ethyl and propyl), a lower alkenyl group (e.g., C_{2-6} alkenyl such as vinyl and allyl), a lower alkynyl group (e.g., C_{2-6} alkynyl such as ethynyl and propargyl), an optionally substituted amino group, an optionally substituted hydroxyl group, a cyano group, an optionally substituted amidino group, a carboxyl group, a lower alkoxycarbonyl group (e.g., C_{1-6} alkoxycarbonyl such as methoxycarbonyl and ethoxycarbonyl), an optionally substituted carbamoyl group (e.g., a carbamoyl group which may be substituted with C_{1-6} alkyl or acyl (e.g., formyl, C_{2-6} alkanoyl, benzoyl, optionally halogenated C_{1-6} alkoxycarbonyl, optionally halogenated C_{1-6} alkylsulfonyl, benzenesulfonyl, etc.), etc.), and an oxo group are preferred, and these substituents may substitute 1 to 3 of any substitutable positions.

X is preferably a C_{1-6} alkylene group, and particularly preferably ethylene.

In the formulas, Z represents –CO-, -SO- or $-SO_2-$.

Z is preferably –CO-.

In the formulas, ring A is an optionally substituted piperazine ring, or an optionally substituted homopiperazine ring.

The substituents which may be carried by the "optionally substituted piperazine ring" and the "optionally substituted homopiperazine ring" represented by ring A include the same groups of the same number as the substituents which may be carried by the "optionally substituted aryl" represented as the substituent for Ar, and an oxo group, a thioxo group and the like.

Ring A is preferably an optionally substituted piperazine ring, and particularly a piperazine ring which may be substituted with one or more substituents selected from a C1-6 alkyl group which may be substituted with a hydroxyl group or an optionally esterified or amidated carboxyl group, and an optionally esterified or amidated carboxyl group.

In the formulas, a is 0, 1 or 2 (preferably, 2).

In the formulas, ring B is an optionally substituted imidazopyridine ring.

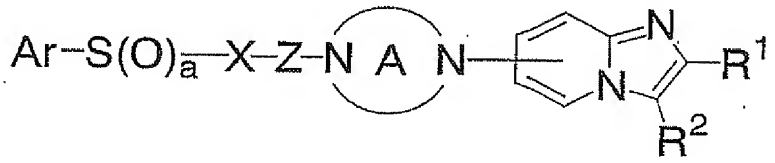
There is no particular limitation on a condensation

manner of an imidazole ring and a pyridine ring in the imidazopyridine ring and, for example, imidazo[1,2-a]pyridine and imidazo[1,5-a]pyridine are preferred and imidazo[1,2-a]pyridine and the like is particularly preferred.

Examples of the substituent for the "optionally substituted imidazopyridine ring" represented by ring B include the same substituents which may be carried by the "optionally substituted naphthyl group", "optionally substituted phenyl group", "optionally substituted indolyl group" and "optionally substituted benzothienyl group" represented by Ar, and these substituents may be substituted at 1 to 5 (preferably, 1 to 3) substitutable positions. Further, substituents for the "optionally substituted imidazopyridine ring" represented by ring B may be bonded to each other to form a ring (e.g., a C_{4-8} cycloalkane ring such as cyclopentane, cyclohexane and cycloheptane, a benzene ring or the like). Among these, an imidazo[1,2-a]pyridine ring which may be substituted with one or more substituents selected from a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted amino group, a nitro group and an optionally esterified or amidated carboxyl group (preferably, an optionally substituted alkyl group, an optionally substituted alkenyl group, an optionally substituted

alkynyl group, an optionally substituted aryl group, an optionally esterified carboxyl group, an amidated carboxyl group, etc.) is preferred and an imidazo[1,2-a]pyridine ring which may be substituted with an optionally substituted C_{1-4} alkyl group is particularly preferred. Nitrogen atoms constituting the imidazopyridine ring may be oxidized.

The imidazo[1,2-a]pyridine ring as ring B may be bonded to ring A at any substitutable positions, and is preferably bonded to ring A at 5-, 6-, 7- or 8-position of the imidazo[1,2-a]pyridine ring. Among these, preferred is a compound represented by the formula (I'):



(I')

wherein R^1 and R^2 each independently represent a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted amino group, a nitro group, or an optionally esterified or amidated carboxyl group (preferably, a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkenyl group, an optionally substituted alkynyl group, an optionally substituted aryl group, an optionally esterified carboxyl group, or an amidated carboxyl group), and R^1 and R^2 may be

bonded to each other to form a ring (e.g., a C_{4-8} cycloalkane ring such as cyclopentane, cyclohexane and cycloheptane, a benzene ring or the like), and other symbols have the same meanings as defined above.

The "optionally substituted hydrocarbon group" as the substituent which may be carried by ring B, and the "hydrocarbon group" in the "optionally substituted hydrocarbon group" represented by R^1 and R^2 includes, for example, a "hydrocarbon group" formed by adding one hydrogen atom to one bond of the "divalent hydrocarbon group" in the "optionally substituted divalent hydrocarbon group" represented by X, and the substituent which may be carried by the "hydrocarbon group" includes the same groups of the same number as the substituents which may be carried by the "divalent hydrocarbon group" in the "optionally substituted divalent hydrocarbon group" represented by X.

The "optionally substituted hydroxyl group" as the substituent which may be carried by ring B, and the substituent which may be carried by the "optionally substituted hydroxyl group" represented by R^1 and R^2 includes, for example, the same substituents which may be carried by the "optionally substituted hydroxyl group" as the substituents which may be carried by the respective "optionally substituted naphthyl group", "optionally substituted phenyl group", "optionally substituted indolyl

group" and "optionally substituted benzothienyl group" represented by Ar.

The "optionally substituted amino group" as the substituent which may be carried by ring B, and the substituent which may be carried out by the "optionally substituted amino group" represented by R^1 and R^2 includes, for example, the same groups of the same number as the substituents which may be carried by the "optionally substituted amino group" as the substituents of the respective "optionally substituted naphthyl group", "optionally substituted phenyl group", "optionally substituted indolyl group" and "optionally substituted benzothienyl group" represented by Ar.

The "optionally esterified or amidated carboxyl group" as the substituent in ring B, and the "optionally esterified or amidated carboxyl group" represented by R^1 and R^2 includes, for example, the same group as the "optionally esterified or amidated carboxyl group" as the substituents which may be carried by the respective "optionally substituted naphthyl group", "optionally substituted phenyl group", "optionally substituted indolyl group" and "optionally substituted benzothienyl group" represented by Ar.

Preferably, the substituent of ring B, and R^1 and R^2 are each independently a hydrogen atom or an optionally

substituted C_{1-4} alkyl group (preferably, a C_{1-4} alkyl group which may be substituted with a hydroxyl group, or an optionally esterified or amidated carboxyl group).

Preferred aspect of the compound represented by the formula (I) in the present invention (hereinafter, may be referred to as a compound (I)) includes, for example, a compound in which the formula (I) is the formula (I'), Ar is a naphthyl group substituted with a halogen atom or an indolyl group substituted with a halogen atom, X is a C_{1-8} alkylene group, Z is -CO-, R^1 and R^2 are each independently a hydrogen atom, a C_{1-4} alkyl group which may be substituted with a hydroxyl group, or an esterified carboxyl group, and a is 2, and 5-[4-[3-[(5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl-2-methylimidazo[1,2-a]pyridine, 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine, 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-(methylaminocarbonyl)methyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine, 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-aminocarbonyl-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine and 1-[3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl]-4-[2-(2-hydroxyethyl)imidazo[1,2-a]pyridin-5-yl]-2-piperazinecarboxamide are particularly preferably used.

A prodrug of the compound (I) refers to a compound

which is converted to the compound (I) by an in vivo reaction caused by an enzyme, gastric acid or the like under physiological conditions, that is, a compound which is converted to the compound (I) upon occurrence of enzymatic oxidation, reduction, hydrolysis or the like, and a compound which is converted to the compound (I) upon occurrence of hydrolysis or the like by gastric acid or the like. Examples of the prodrug of the compound (I) include compounds obtained by acylation, alkylation or phosphorylation of the amino group of the compound (I) (for example, the compounds in which the amino group of the compound (I) is in the form of eicosanoyl, alanyl, pentylaminocarbonyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonyl, tetrahydrofuranyl, pyrrolidylmethyl, pivaloyloxymethyl, tert-butyl or the like); compounds obtained by acylation, alkylation, phosphorylation or boration of the hydroxyl group of the compound (I) (for example, the compounds in which the hydroxyl group of the compound (I) is in the form of acetyl, palmitoyl, propanoyl, pivaloyl, succinyl, fumaryl, alanyl, dimethylaminomethylcarbonyl or the like); compounds resulting from esterification or amidation of the carboxyl group of the compound (I) (for example, the compounds in which the carboxyl group of the compound (I) is in the form of ethyl ester, phenyl ester, carboxymethyl ester,

dimethylaminomethyl ester, pivaloyloxymethyl ester, ethoxycarbonyloxyethyl ester, phthalidyl ester, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, 1-(cyclohexyloxycarbonyloxyethyl ester, methylamide or the like); or the like. These compounds can be prepared from the compound (I) by methods known per se in the art.

Furthermore, the prodrug of the compound (I) may also be also a compound which is converted to the compound (I) under physiological conditions, as described in "Development of Pharmaceutical Products", Vol. 7, Design of Molecules, Hirokawa Publisher, pp.163-198 (1990).

Examples of the salt of the compound (I) include pharmaceutically acceptable salts or the like, for example, acid addition salts with acids such as trifluoroacetic acid, acetic acid, lactic acid, succinic acid, maleic acid, tartaric acid, citric acid, gluconic acid, ascorbic acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, cinnamic acid, fumaric acid, phosphonic acid, hydrochloric acid, nitric acid, hydrobromic acid, hydroiodic acid, sulfamic acid and sulfuric acid; salts with metals such as sodium, potassium, magnesium and calcium; organic salts such as trimethylamine, triethylamine, pyridine, picoline, N-methylpyrrolidine, N-methylpiperidine and N-methylmorpholine.

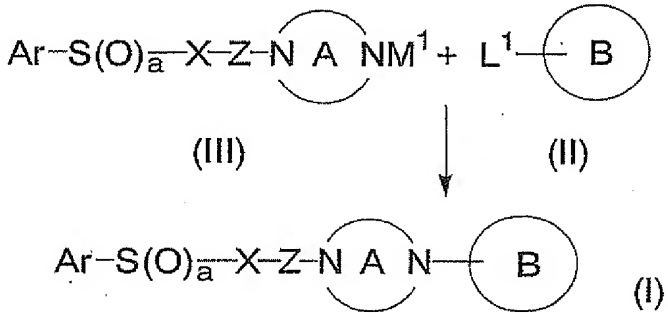
When an optically active form of the compound (I) is

needed, for example, an optically active form can be obtained by using an optically active starting material, or by resolving a racemate of the compound using conventional methods.

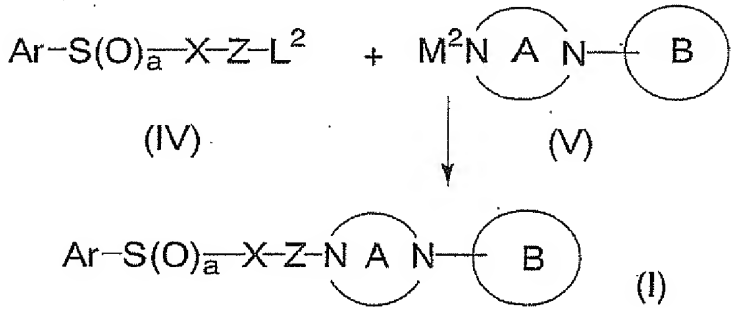
The compound (I) may be labeled with such as isotopes (for example, ^{3}H, ^{14}C, ^{35}S, ^{125}I, etc.)

The compound (I) can be prepared by, for example, the following processes A to D. Each of the compounds described in the following reaction scheme may be in a salt form as long as the reaction is not adversely affected, and such a salt may be exemplified by the same ones as the salts of the compound represented by the formula (I).

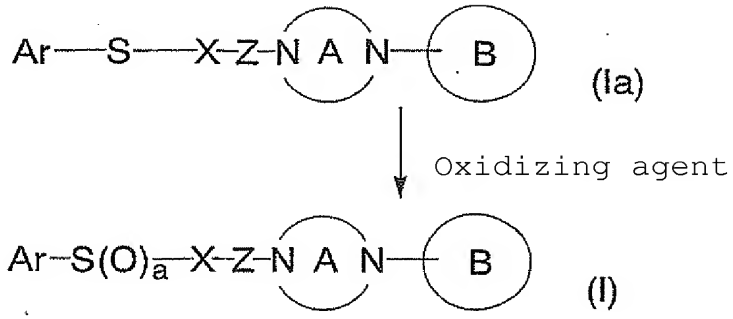
[Process A]



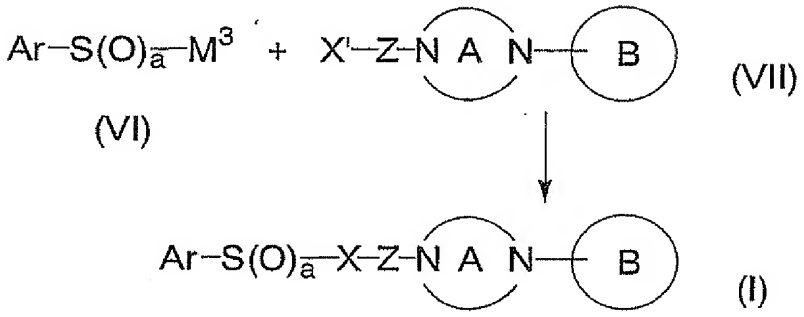
[Process B]



[Process C]

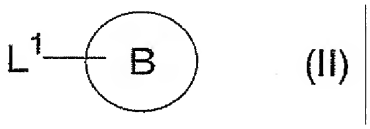


[Process D]



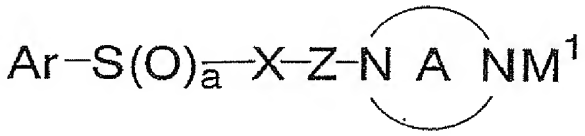
[Process A]

The compound (I) can be prepared by reacting a compound (II) represented by the formula (II):



wherein L^1 represents a leaving group (for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), or a group forming a reactive derivative of sulfonic acid (e.g., sulfonic acid ester, active sulfonic acid amide (e.g., 1,2,4-triazolide, imidazolide, etc.), a quaternary aminesulfonyl product (e.g., an N-methylpyrrolidinium salt,

etc.), bis-sulfonylimide (e.g., N-phenylbis-sulfonylimide, etc.), etc.), or the like), and the other symbols have the same meanings as defined above, or a salt thereof with a compound (III) represented by the formula (III):



(III)

wherein M^1 represents a hydrogen atom, an alkali metal (e.g., lithium, potassium, sodium, cesium, etc.), an alkali earth metal (e.g., calcium, magnesium, etc.) or a leaving group (e.g., trimethylsilyl group, etc.), and the other symbols have the same meanings as defined above, or a salt thereof. Examples of the salt of the compound (II) or the compound (III) include acid addition salts of acids that form acid addition salts and the compound (I).

The present reaction is generally carried out in a solvent, and a solvent which does not obstruct the reaction is appropriately selected. For the solvent, alcohols (e.g., methanol, ethanol, propanol, isopropanol, butanol, tert-butanol, etc.), ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether, ethylene glycol-dimethyl ether, etc.), esters (e.g., ethyl formate, ethyl acetate, n-butyl acetate, etc.), carboxylic acids (e.g., formic acid, acetic acid, propionic acid, etc.), halogenated hydrocarbons (e.g., dichloromethane,

chloroform, carbon tetrachloride, trichloroethylene, 1,2-dichloroethane, chlorobenzene, etc.), hydrocarbons (e.g., n-hexane, benzene, toluene, etc.), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, etc.), ketones (e.g., acetone, methyl ethyl ketone, methyl isobutyl ketone, etc.), nitriles (e.g., acetonitrile, propionitrile, etc.) and the like, as well as dimethyl sulfoxide, sulfolane, hexamethyl phosphoramide, water and the like are used individually or as mixed solvents.

The present reaction may be carried out in the presence of a base, if necessary, and examples of the base include inorganic bases such as lithium hydroxide, potassium hydroxide, sodium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and potassium hydrogen carbonate; alkali metal salts of a C_{1-6} lower fatty acid, such as sodium formate, sodium acetate and potassium acetate; or tertiary amines such as triethylamine, tri(n-propyl)amine, tri(n-butyl)amine, diisopropylethylamine, cyclohexyldimethylamine, pyridine, lutidine, γ-collidine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine and N-methylmorpholine.

The present reaction is carried out by using 0.5 to 5 equivalents, and preferably 0.8 to 2 equivalents, of the compound (II) based on the compound (III).

The reaction temperature is from -20 to 200°C, and preferably from 0 to 170°C.

The reaction time may vary depending on the kind of the compound (II) or compound (III), kind of the solvent, reaction temperature or the like, but is usually from about 1 minute to about 72 hours, and preferably from about 15 minutes to about 24 hours.

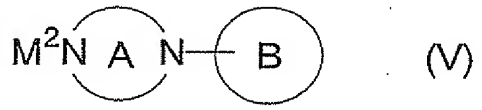
[Process B]

The compound (I) can be prepared by reacting a compound (IV) represented by the formula (IV):

$$Ar\text{-}S(O)_a\text{-}X\text{-}Z\text{-}L^2 \qquad (IV)$$

wherein L^2 represents a leaving group (for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a C_{1-6} alkylsulfonyloxy group which may be substituted with 1 to 3 halogen atoms (e.g., methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy, etc.), an optionally substituted arylsulfonyloxy group (e.g., benzenesulfonyloxy, p-toluenesulfonyloxy, p-bromobenzenesulfonyloxy, etc.), or a group capable of reacting with a hydroxyl group to form free carboxylic acid, a salt thereof (e.g., inorganic salt, organic salt, etc.) or a reactive derivative thereof (e.g., acid halide, ester, acid azide, acid anhydride, mixed acid anhydride, active amide, active ester, active thioester, etc.), and the other symbols have the same meanings as

defined above (a compound in which L^2 is a hydroxyl group is referred to as a free acid (IV')), with a compound (V) represented by the formula (V):



(V)

wherein M^2 represents a hydrogen atom, an alkali metal (e.g., lithium, potassium, sodium, cesium, etc.), an alkali earth metal (e.g., calcium, magnesium, etc.) or a leaving group, and the other symbols have the same meanings as defined above.

The present process is carried out by reacting the compound (V) or a salt thereof with a free acid (IV') or a salt thereof (e.g., an inorganic salt, an organic salt, etc.) or a reactive derivative thereof (e.g., acid halide, ester, acid azide, acid anhydride, mixed acid anhydride, active amide, active ester, active thioester, etc.). Examples of the salt of the compound (V) include acid addition salts of acids forming acid addition salts and the compound (I).

Examples of the inorganic salt used for the compound (IV) include alkali metal salts (e.g., sodium salts, potassium salts, etc.) alkaline earth metal salts (e.g., calcium salts, etc.) and the like, while examples of the organic salts to be used include trimethylamine salts, triethylamine salts, tert-butyldimethylamine salts,

dibenzylmethylamine salts, benzyldimethylamine salts, N,N-dimethylaniline salts, pyridine salts, quinoline salts and the like. Examples of the acid halide include acid chloride, acid bromide and the like, while examples of the ester include lower alkyl esters such as methyl and ethyl. Examples of the mixed acid anhydride include mono-C_{1-4} alkyl carbonate mixed acid anhydrides (e.g., mixed acid anhydrides of free acid (IV') with monomethyl carbonate, monoethyl carbonate, monoisopropyl carbonate, monoisobutyl carbonate, mono-tert-butyl carbonate, monobenzyl carbonate, mono(p-nitrobenzyl) carbonate, monoallyl carbonate, etc.), C_{1-6} aliphatic carboxylic acid mixed acid anhydrides (e.g., mixed acid anhydrides of free acid (IV') with acetic acid, cyanoacetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, pivalic acid, trifluoroacetic acid, trichloroacetic acid, acetoacetic acid, etc.), C_{7-11} aromatic carboxylic acid mixed acid anhydrides (e.g., mixed acid anhydrides of free acid (IV') with benzoic acid, p-toluyl acid, p-chlorobenzoic acid, etc.), organic sulfonic acid mixed acid anhydrides (e.g., mixed acid anhydrides of methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.) and the like. Examples of the active amide include an amide with a nitrogen-containing heterocyclic compound (e.g., acid amides of free acid (IV')

with pyrazole, imidazole, benzotriazole and the like, and these nitrogen-containing heterocyclic compounds may be substituted with C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.), C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, etc.), a halogen atom (for example, fluorine, chlorine, bromine, etc.), oxo, thioxo, C_{1-6} alkylthio (e.g., methylthio, ethylthio, propylthio, butylthio, etc.), etc.).

Examples of the active ester include organic phosphoric acid esters (e.g., diethoxyphosphoric acid ester, diphenoxyphosphoric acid ester, etc.), as well as p-nitrophenyl ester, 2,4-dinitrophenyl ester, cyanomethyl ester, pentachlorophenyl ester, N-hydroxysuccinimide ester, N-hydroxyphthalimide ester, 1-hydroxybenzotriazole ester, 6-chloro-1-hydroxybenzotriazole ester, 1-hydroxy-1H-2-pyrridone ester and the like. Examples of the active thioester include esters with aromatic heterocyclic thiol compounds [these heterocycles may be substituted with C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.), C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, etc.), a halogen atom (e.g., fluorine, chlorine, bromine, etc.), C_{1-6} alkylthio (e.g., methylthio, ethylthio, propylthio, butylthio, etc.), or the like] [e.g., 2-

pyridylthiol ester, 2-benzothiazolylthiol ester] and the like.

The present reaction is generally carried out in a solvent, and if necessary, is carried out in the presence of a base or a condensing agent (e.g., carbodiimide (DCC, WSC, DIC, etc.), a phosphoric acid derivative (e.g., diethyl cyanophosphate, DPPA, BOP-Cl, etc.), 4-(4,6-dimethoxy-1,3-5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM: Kunishima et al., Tetrahedron, 1999, 55, 13159), etc.). The solvent and base to be used for the present invention, the same solvents and bases mentioned for process A are used.

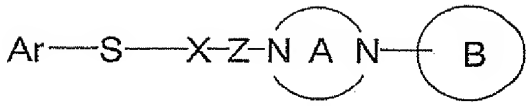
The reaction is carried out by using 0.5 to 5 equivalents, and preferably 0.8 to 2 equivalents, of the compound (V) based on the compound (V).

The reaction temperature is from -50 to 150°C, and preferably from -20 to 100°C.

The reaction time may vary depending on the kind of the compound (IV) or compound (V), kinds of the solvent and base, reaction temperature or the like, but is usually from about 1 minute to about 100 hours, and preferably from about 15 minutes to about 48 hours.

[Process C]

The compound (I) can be prepared by oxidizing a compound (Ia) represented by the formula (Ia):



(Ia)

wherein symbols have the same meaning as defined above, or a salt thereof.

The present oxidation reaction is carried out in the presence of an oxidizing agent. Here, examples of the oxidizing agent include oxygen, hydrogen peroxide, an organic peracid such as perbenzoic acid, m-chloroperbenzoic acid and peracetic acid; a perchlorate such as lithium perchlorate, silver perchlorate and tetrabutylammonium perchlorate; a periodate such as odium periodate; periodic acid; manganese dioxide; lead tetraacetate; a permanganate such as potassium permanganate; halogen such as iodine, bromine, chlorine or the like; N-bromosuccinic acid imide, N-chlorosuccinic acid imide, sulfuryl chloride, chloramine T and the like.

The present reaction is generally carried out in a solvent, and a solvent which does not obstruct the reaction is appropriately selected. For the solvent, alcohols (e.g., methanol, ethanol, propanol, isopropanol, butanol, tert-butanol, etc.), ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether, ethylene glycol-dimethyl ether, etc.), esters (e.g., ethyl formate, ethyl acetate, n-butyl acetate, etc.), carboxylic acids (e.g., formic acid, acetic acid, propionic acid,

etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, trichloroethylene, 1,2-dichloroethane, chlorobenzene, etc.), hydrocarbons (e.g., n-hexane, benzene, toluene, etc.), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide, etc.), ketones (e.g., acetone, methyl ethyl ketone, methyl isobutyl ketone, etc.), nitriles (e.g., acetonitrile, propionitrile, etc.) and the like, as well as sulfolane, hexamethyl phosphoramide, water and the like are used individually or as mixed solvents.

The present reaction can be carried out in the presence of a base. For the base, inorganic bases, for example, alkali metal hydroxides such as lithium hydroxide, sodium hydroxide and potassium hydroxide; alkali earth metal hydroxides such as magnesium hydroxide and calcium hydroxide; alkali metal carbonates such as sodium carbonate and potassium carbonate; alkali metal hydrogen carbonates such as sodium hydrogen carbonate and potassium hydrogen carbonate are used.

The reaction is carried out by using 0.1 to 20 equivalents, and preferably about 0.4 to 10 equivalents, of the oxidizing agent, and 0.1 to 20 equivalents, preferably 0.4 to 10 equivalents of the base, based on the compound (Ia).

The present reaction may be carried out in the

presence of an acid, if necessary, and for the acid, mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and perchloric acid; sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid and camphorsulfonic acid; and organic acids such as formic acid, acetic acid, propionic acid and trifluoroacetic acid are used. The amount of these acids to be used is from 0.1 to 20 equivalents, and preferably from 0.5 to 10 equivalents, based on the compound (Ia).

The reaction temperature is about -10°C to about 250°C, and preferably about -5°C to about 150°C.

The reaction time may vary depending on the kind of the compound (Ia), base or solvent, reaction temperature or the like, but is usually about 1 minute to about 50 hours, preferably about 5 minutes to about 24 hours.

[Process D]

The compound (I) can be prepared by reacting a compound (VII) represented by the formula (VI):

$$Ar\text{-}S(O)_a\text{-}M^3 \qquad (VI)$$

wherein M^3 represents a hydrogen atom, a hydroxyl group, an alkali metal (e.g., lithium, potassium, sodium, cesium, etc.), an alkali earth metal (e.g., calcium, magnesium, etc.) or a leaving group (e.g., trimethylsilyl group, etc.), and the other symbols have the same meanings as defined in

claim 1, or a salt thereof, with a compound (VII) represented by the formula (VII):

(VII)

wherein X' represents alkenyl or alkynyl (preferably, C_{2-8} alkenyl or C_{2-8} alkynyl), or alkyl having a leaving group (e.g., a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a C_{1-6} alkylsulfonyloxy group which may be substituted with 1 to 3 halogen atoms (e.g., methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy, etc.), an optionally substituted arylsulfonyloxy group (e.g., benzenesulfonyloxy, p-toluenesulfonyloxy, p-bromobenzenesulfonyloxy, etc.), a hydroxyl group, etc.) (preferably, C_{1-8} alkyl); and the other symbols have the same meanings as defined above.

The present process is generally carried out in a solvent, and if necessary, is carried out in the presence of a base. For the solvent and base, the same ones as the solvents and bases mentioned for Process A are used.

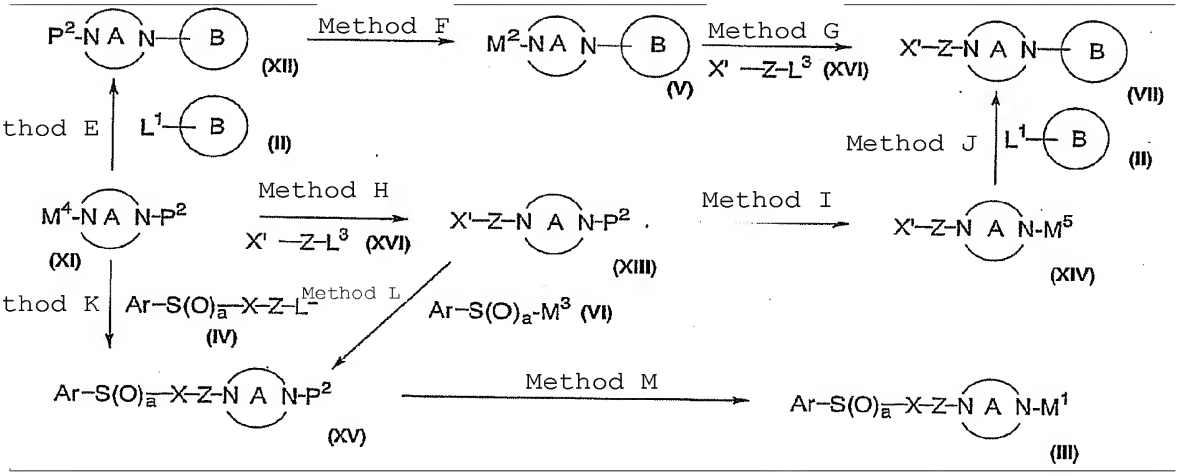
The reaction is carried out by using 0.5 to 3 equivalents, and preferably 0.8 to 2 equivalents, of the compound (VI) based on the compound (VII).

The reaction temperature is from -50 to 150°C, and preferably from -20 to 120°C.

The reaction time may vary depending on the kind of

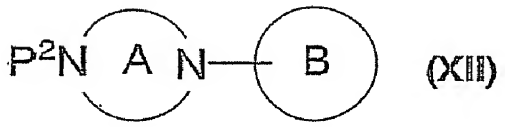
the compound (VI) or compound (VII), kinds of the solvent and base, reaction temperature or the like, but is usually from about 1 minute to about 100 hours, and preferably from about 15 minutes to about 24 hours.

The starting material compounds (III), (V) and (VII) used in each of the above reactions can be synthesized by, for example, the following processes.



[Process E]

A compound (XII) represented by the formula (XII):



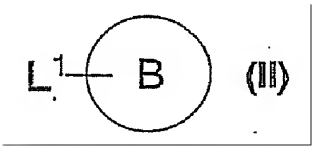
(XII)

or a salt thereof can be prepared by reacting a compound (XI) represented by the formula (XI):

(XI)

wherein P^2 represents a protective group for an amino group,

M^4 represents a hydrogen atom, an alkali metal (e.g., lithium, potassium, sodium, cesium, etc.), an alkali earth metal (e.g., calcium, magnesium, etc.) or a leaving group (e.g., trimethylsilyl group, etc.), and the other symbols have the same meanings as defined above, or a salt thereof, with a compound (II) represented by the formula (II):

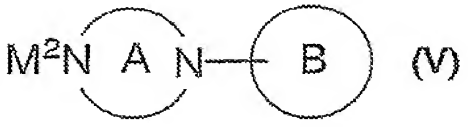


wherein symbols have the same meanings as defined above, or a salt thereof.

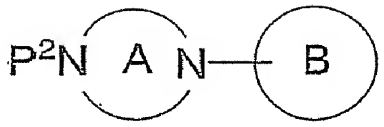
The present reaction is carried out according to the reaction conditions, reaction solvent, reaction time and the like described in the reaction between the compound (II) and the compound (III) for process A, or a process equivalent thereto.

[Process F]

The compound (V) represented by the formula (V):



wherein symbols have the same meanings as defined above, or a salt thereof can be prepared by eliminating a protective group for an amino group from the compound (XII) represented by the formula (XII):



(XII)

wherein symbols have the same meanings as defined above, or a salt thereof, or converting a hydrogen atom on the amino group obtained by deprotection to an alkali metal, an alkali earth metal or a leaving group.

For the protective group for an amino group, optionally substituted C_{1-6} alkylcarbonyl (e.g., formyl, acetyl, ethylcarbonyl, etc.), phenylcarbonyl, C_{1-6} alkyl-oxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, etc.), C_{6-10} aryloxycarbonyl (e.g., phenoxycarbonyl, etc.), C_{7-10} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, etc.), trityl, phthaloyl and the like are used. These protective groups may be substituted with about 1 to 4 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkyl-carbonyl (e.g., acetyl, ethylcarbonyl, butylcarbonyl, etc.), a nitro group and the like.

The method of eliminating the protective group for the amino group can be carried out, for example, according to the method described in T. W. Green et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, or a method equivalent thereto. For example, methods of using an acid, a base, reduction, ultraviolet ray, palladium acetate and the like are used.

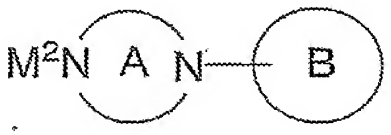
The method of converting a hydrogen atom on the amino group to an alkali metal, an alkali earth metal or a leaving group can be carried out, for example, according to the methods described in S. Patai et al., "The chemistry of functional groups, Supplement F2, The chemistry of amino, nitroso, nitro, and related compounds Part 1", 1996, John Wiley & Sons, Inc., New York and S. Patai et al., "The chemistry of functional groups, Supplement F2, The chemistry of amino, nitroso, and related compounds Part 2", 1996, John Wiley & Sons, Inc., New York, or a method equivalent thereto. For example, methods of using sodium hydride, methyl magnesium bromide, N-trimethylsilylacetamide or the like are used.

[Process G]

The compound (VII) represented by the formula (VII):

(VII)

wherein symbols have the same meanings as defined above, or a salt thereof can be prepared by reacting the compound (V) represented by the formula (V):



(V)

wherein symbols have the same meanings as defined above, or a salt thereof, with a compound (XVI) represented by the

formula (XVI):

$X'-Z-L^3$ (XVI)

wherein L^3 represents a leaving group, and symbols have the same meanings as defined above, or a salt thereof.

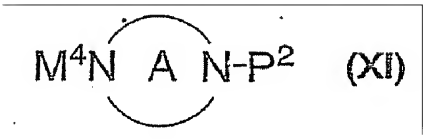
For the leaving group represented by L^3, the same leaving group represented as L^2 is used.

The reaction conditions, reaction solvent, reaction time and the like in the present reaction are set according to the same reaction conditions and the like described in the reaction between the compound (IV) and the compound (V) for process B, or a process equivalent thereto.

[Process H]

A compound (XIII) represented by the formula (XIII):

wherein symbols have the same meanings as defined above, or a salt thereof can be prepared by reacting the compound (XI) represented by the formula (XI):



wherein symbols have the same meanings as defined above, or a salt thereof, with the compound (XVI) represented by the formula (XVI):

$X'-Z-L^3$ (XVI)

wherein symbols have the same meanings as defined above, or a salt thereof.

The present reaction is carried out according to the same reaction conditions, reaction solvent, reaction time and the like described in the reaction between the compound (IV) and the compound (V) for process B, or a process equivalent thereto.

[Process I]

A compound (XIV) represented by the formula (XIV):

wherein M^5 represents a hydrogen atom, an alkali metal (e.g., lithium, potassium, sodium, cesium, etc.), an alkali earth metal (e.g., calcium, magnesium, etc.) or a leaving group (e.g., trimethylsilyl group, etc.), and the other symbols have the same meanings as defined above, or a salt thereof can be prepared by eliminating a protective group for an amino group from the compound (XIII) represented by the formula (XIII):

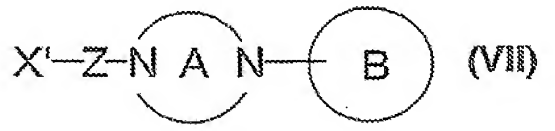
wherein symbols have the same meanings as defined above, or a salt thereof, or converting a hydrogen atom on the amino

group obtained by deprotection to an alkali metal, an alkali earth metal or a leaving group.

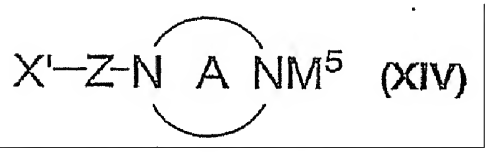
The reaction conditions, reaction solvent, reaction time and the like in the present reaction are set according to the reaction conditions and the like described in the deprotection reaction of the compound (XII) for process F, or a process equivalent thereto.

[Process J]

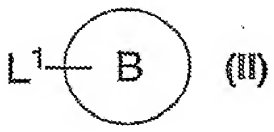
The compound (VII) represented by the formula (VII):



wherein symbols have the same meanings as defined above, or a salt thereof can be prepared by reacting the compound (XIV) represented by the formula (XIV):



wherein symbols have the same meanings as defined above, or a salt thereof, with the compound (II) represented by the formula (II):

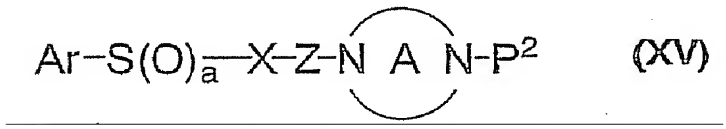


wherein symbols have the same meanings as defined above, or a salt thereof.

The reaction conditions, reaction solvent, reaction time and the like in the present reaction are set according to the reaction conditions and the like described in the reaction between the compound (II) and the compound (III) for process A, or a process equivalent thereto.

[Process K]

A compound (XV) represented by the formula (XV):



wherein symbols have the same meanings as defined above, or a salt thereof can be prepared by reacting the compound (XI) represented by the formula (XI):

wherein symbols have the same meanings as defined above, or a salt thereof, with the compound (IV) represented by the formula (IV):

$Ar\text{-}S(O)a\text{-}X\text{-}L^2$ (IV)

wherein symbols have the same meanings as defined above, or a salt thereof.

The reaction conditions, reaction solvent, reaction time and the like in the present reaction are set according to the reaction conditions and the like described in the reaction between the compound (IV) and the compound (V) for process B, or a process equivalent thereto.

[Process L]

The compound (XV) represented by the formula (XV):

(XV)

wherein symbols have the same meanings as defined above can be prepared by reacting the compound (XIII) represented by the formula (XIII):

(XIII)

wherein symbols have the same meanings as defined above, or a salt thereof, with the compound (VI) represented by the formula (VI):

$Ar\text{-}S(O)a\text{-}M^3$ (VI)

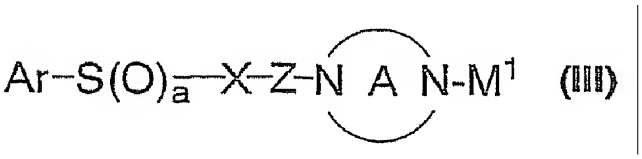
wherein symbols have the same meanings as defined above, or a salt thereof.

If necessary, the oxidation number of sulfur atoms can be increased by oxidizing the product.

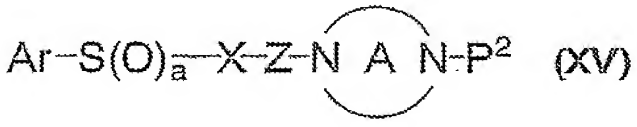
The reaction conditions, reaction solvent, reaction time and the like in the present reaction are set according to the reaction conditions, reaction solvent and the like described in the reaction between the compound (VI) and the compound (VII) for process D, or a process equivalent thereto. The reaction conditions, reaction solvent, reaction time and the like in the oxidation reaction of sulfur atoms are set according to the oxidizing agent, reaction conditions, reaction solvent and the like described in the oxidation reaction of the compound (Ia) for process C, or a process equivalent thereto.

[Process M]

The compound (III) represented by the formula (III):



wherein symbols have the same meanings as defined above, or a salt thereof can be prepared by eliminating a protective group for an amino group from the compound (XV) represented by the formula (XV):



wherein symbols have the same meanings as defined above, or a salt thereof, or converting a hydrogen atom on the amino

group obtained by deprotection to an alkali metal, an alkali earth metal or a leaving group.

The reaction conditions, reaction solvent, reaction time and the like in the present reaction are set according to the reaction conditions and the like described in the deprotection reaction of the compound (XII) for process F, or a process equivalent thereto.

The starting material compound (II) used in each of the above processes A to M can be prepared by, for example, the methods described in JP 5-051383 A, JP 5-039221 A, EP 471236 A specification, European Journal of Medicinal Chemistry, Chimica Therapeutica, 1978, Vol. 13, No. 3, p.271-276, or a method equivalent thereto. The other starting material compounds (IV), (VI), (XI) and (XVI) can be prepared by methods known per se in the art (for example, method described in WO 02/06234), or a method equivalent thereto.

When the compounds are obtained in their free forms by the reactions of the present invention, the compounds may be converted to salt forms according to conventional methods, and when the compounds are obtained in salt forms, the compounds may be converted to free products or other salts according to conventional methods.

Among synthetic intermediates used in the above

reactions, 3-(5-halogeno-2-indolyl)sulfonylpropionic acid, an ester thereof or an amide thereof, or a salt thereof [preferably, 3-(5-chloro-2-indolyl)sulfonylpropionic acid, an ester thereof or an amide thereof, or a salt thereof] and 3-(1-tert-butoxycarbonyl-5-halogeno-2-indolyl)sulfonylpropionic acid, an ester thereof or an amide thereof, or a salt thereof [preferably, 3-(1-tert-butoxycarbonyl-5-chloro-2-indolyl)sulfonylpropionic acid, an ester thereof or an amide thereof, or a salt thereof] are novel compounds and are advantageously used to synthesize the compound (I).

The salt may be any salt which does not obstruct the reaction and includes, for example, the same salts as those used in the compound (I).

The ester may be any ester which does not obstruct the reaction and includes, for example, (1) lower alkyl C_{1-6} esters such as methyl, ethyl and tert-butyl, (2) organic phosphoric acid esters (e.g., diethoxyphosphoric acid ester, diphenoxyphosphoric acid ester, etc.), (3) p-nitrophenyl ester, (4) 2,4-dinitrophenyl ester, (5) cyanomethyl ester, (6) pentachlorophenyl ester, (7) N-hydroxysuccinimide ester, (8) N-hydroxyphthalimide ester, (9) 1-hydroxybenzotriazole ester, (10) 6-chloro-1-hydroxybenzotriazole ester, (11) 1-hydroxy-1H-2-pyrridone ester, (12) thioester [e.g., esters with aromatic heterocyclic thiol compounds [these

heterocycles may be substituted with C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.), C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, etc.), a halogen atom (e.g., fluorine, chlorine, bromine, etc.), C_{1-6} alkylthio (e.g., methylthio, ethylthio, propylthio, butylthio, etc.) and the like] [e.g., 2-pyridylthiol ester, 2-benzothiazolylthiol ester, etc.].

The amide may be any amide which does not obstruct the reaction and includes, for example, amides with nitrogen-containing heterocyclic compounds (e.g., acid amides with pyrazole, imidazole, benzotriazole or the like and these nitrogen-containing heterocyclic compounds may be substituted with C_{1-6} alkyl (e.g., methyl, ethyl propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.), C_{1-6} alkoxy (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, etc.), halogen atom (for example, fluorine, chlorine, bromine, etc.), oxo, thioxo, C_{1-6} alkylthio (e.g., methylthio, ethylthio, propylthio, butylthio, etc.), etc.).

3-(5-halogeno-2-indolyl)sulfonylpropionic acid, an ester thereof or an amide thereof, or a salt thereof, and 3-(1-tert-butoxycarbonyl-5-halogeno-2-indolyl)sulfonylpropionic acid, an ester thereof or an amide thereof, or a salt thereof may be used for the

reaction for synthesizing the compound (I) after converting to an acid halide, a mixed acid anhydride or the like. Examples of the acid halide include acid chloride, acid bromide and the like, while examples of the mixed acid anhydride include mono-C_{1-4} alkyl carbonate mixed acid anhydrides (e.g., mixed acid anhydrides with monomethyl carbonate, monoethyl carbonate, monoisopropyl carbonate, monoisobutyl carbonate, mono-tert-butyl carbonate, monobenzyl carbonate, mono(p-nitrobenzyl) carbonate, monoallyl carbonate, etc.), C_{1-6} aliphatic carboxylic acid mixed acid anhydrides (e.g., mixed acid anhydrides with acetic acid, cyanoacetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, pivalic acid, trifluoroacetic acid, trichloroacetic acid, acetoacetic acid, etc.), C_{7-11} aromatic carboxylic acid mixed acid anhydrides (e.g., mixed acid anhydrides with benzoic acid, p-toluyl acid, p-chlorobenzoic acid, etc.), organic sulfonic acid mixed acid anhydrides (e.g., mixed acid anhydrides with methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid or the like) and the like.

The compound (I) thus obtained can be isolated and purified from the reaction mixture by means that are known per se, for example, by using means such as extraction, concentration, neutralization, filtration,

recrystallization, column chromatography and thin layer chromatography.

The salt of the compound (I) can be prepared by means that are known per se, for example, by adding an inorganic acid or an organic acid to the compound (I).

When the compound (I) is obtained as optical isomers, these individual optical isomers and mixtures thereof are all naturally included in the scope of the present invention, and if desired, these isomers can be optically resolved according to methods known per se, or can be prepared individually.

The compound (I) or a salt thereof may also be a hydrate, and hydrates and anhydrates are all included in the scope of the present invention.

The compound (I) or a salt thereof of the present invention is safe with low toxicity and inhibits FXa, and also has anticoagulation effect, and therefore it is useful for preventing and treating various arterial and venous thrombosis of animals, in particular mammals (e.g., human being, monkey, cat, pig, horse, cattle, mouse, rat, guinea pig, dog, rabbit, etc.), for example, myocardial infarction, cerebral infarction, deep vein thrombosis, pulmonary thromboembolism or atherosclerotic obliterans, economy-class syndrome, thromboembolism during and post operation, and the following disorders. Among these, it is preferably

used for preventing and treating ischemic cerebral infarction (in particular, thromboembolic stroke due to atrial fibrillation, etc., and ischemic cerebral infarction caused by progression of atherosclerosis or activation of blood coagulation system), deep vein thrombosis, pulmonary thromboembolism or the like.

Brain:

Prevention or treatment of cerebral infarction, ischemic cerebrovascular disorder, thromboembolic stroke caused by atrial fibrillation, heart failure, valvular disease, or the like, acute ischemic cerebral apoplexy, acute stage cerebral thrombosis, cerebrovascular contraction after subarachnoid hemorrhage, Alzheimer's disease, transient ischemic attack (TIA), mixed dementia, cerebrovascular dementia, asymptomatic/multiple cerebral infarction, lacunar infarction and the like, prognosis improvement or secondary onset prevention of cerebral infarction, prevention or treatment of thrombus after an extracranial and intracranial arterial bypass operation, combination use or supplemental use with a thrombolytic agent against cerebral infarction (particularly, ischemic cerebrovascular disorder), combination therapy with an anti-platelet drug such as aspirin in preventing onset of cerebral infarction.

Heart:

Prevention or treatment of acute coronary disease such

as acute myocardial infarction, myocardial infarction, ischemic coronary disease, unstable angina, myocardiopathy, acute heart failure, congestive chronic heart failure, valvular disease and the like, prognosis improvement or secondary onset prevention of acute coronary disease such as angina, prevention or treatment of thrombus formation after artificial valve or artificial heart replacement, prevention or treatment of vascular reocclusion and restenosis after stent indwelling or PTCA (percutaneous transluminal coronary angioplasty) or coronary intervention such as atherectomy, prevention or treatment of vascular reocclusion and restenosis after coronary bypass operation, combination use or supplemental use with a thrombolytic agent against acute coronary disease, combination therapy with an anti-platelet drug such as aspirin in preventing onset of myocardial infarction.

Periphery:

Prevention or treatment of deep vein thrombosis, chronic arterial obliterans, atherosclerotic obliterans, peripheral circulation failure such as Buerger's disease, peripheral circulation failure after frostbite, aneurysm, varix, adult respiratory distress syndrome, acute renal failure, chronic renal disease (e.g., diabetic nephropathy, chronic glumerular nephritis, IgA nephropathy, etc.), diabetic circulation disorder, pain, nerve disorder,

diabetic complication such as diabetic retinopathy and the like, prognosis improvement or secondary onset prevention of deep vein thrombosis, prevention or treatment of deep vein thrombosis or pulmonary thromboembolism after a joint operation including total hip arthroplasty (THA) or total knee arthroplasty (TKA), prevention or treatment of deep vein thrombosis or pulmonary thromboembolism after an orthopedic, plastic surgical or general surgical operation including a spine operation, prevention or treatment of thrombus after a peripheral vascular bypass operation or artificial vessel or vena cava filter indwelling, prevention or treatment of vascular reocclusion and restenosis after stent indwelling or PTA (percutaneous transluminal angioplasty) or peripheral vascular intervention such as atherectomy, prevention or treatment of deep vein thrombosis or pulmonary thromboembolism accompanied with acute internal disease, combination use or supplemental therapy with a thrombolytic agent against deep vein thrombosis and pulmonary thromboembolism, combination therapy with an anti-platelet drug such as aspirin in therapy of peripheral circulation failure such as arteriosclerotic obliterans.

Others:

Prevention or treatment of pulmonary embolism, acute pulmonary embolism, economy-class syndrome,

thrombocytopenia or activation of blood coagulation system or complement activation caused by dialysis, thrombocytopenia on a major operation, thrombocytopenic purpura, disseminated intravascular coagulation syndrome (DIC) developed in a patient suffering from progression of arteriosclerosis, cancer metastasis, systemic inflammatory reaction syndrome (SIRS), pancreatitis, cancer, leukemia, a major operation or sepsis or the like, various organ disorders such as liver function disorder caused by oligemia, ischemia or retention of blood, various organ failures caused by progression of shock or DIC (e.g. lung failure, liver failure, kidney failure, heart failure, etc.), systemic lupus erythematosus, diffuse collagen disease, hyperthyroidism, puerperal palsy and the like, inhibition of rejective response on transplantation, organ protection or function improvement on transplantation, prevention of perfusion blood coagulation during blood extracorporeal circulation, substitute therapeutic use against development of thrombocytopenia caused by heparin administration, promotion of bedsore or wound healing, inhibition of activation of blood excessive coagulation reaction on various hormone supplement therapy, substitute therapeutic use for a patient resistant or contraindicative to a coumarin drug including warfarin, inhibition of activation of excessive coagulation reaction on

administration of a blood preparation or a blood coagulation factor-containing preparation and the like.

The compound (I) or a salt thereof of the present invention can be administered orally or parenterally, as it is or as a mixture with a pharmaceutically acceptable carrier.

Examples of the preparation of the present invention, which contains the compound (I) or a salt thereof, as a formulation for oral administration include a tablet (including sugar-coated tablet and film-coated tablet), a pill, a granule, a powder, a capsule (including soft capsule and microcapsule), a syrup, an emulsion, a suspension and the like; and as a formulation for parenteral administration, include an injectable preparation, an infusion, a drip infusion, a suppository and the like. It is also effective for the preparation to be provided as combination sustained release preparations with suitable bases (e.g., polymers of butyric acid, polymers of glycolic acid, copolymers of butyric acid-glycolic acid, a mixture of polymers of butyric acid and polymers of glycolic acid, polyglycerol fatty acid esters, etc.).

The content of the compound (I) or a salt thereof in the preparation of the present invention may vary depending on the form of the preparation, but is usually from 2 to

85% by weight, and preferably from 5 to 70% by weight, based on the total preparation.

For the process of preparing the compound (I) or a salt thereof in the formulations, it is possible to apply known preparation methods that are generally used in the related art. When the formulations are prepared, it is possible, if necessary, to prepare the formulations by suitably adding appropriate amounts of excipients, binding agents, disintegrants, lubricants, sweeteners, surfactants, suspending agents, emulsifying agents and the like that are conventionally used in the art of pharmaceutical preparation.

For example, when the compound (I) or a salt thereof is prepared into a tablet, preparation can be carried out by adding excipients, binding agents, disintegrants, lubricants and the like; while when prepared into a pill or a granule, preparation can be carried out by adding excipients, binding agents, disintegrants and the like. When prepared into a powder or a capsule, preparation can be carried out by adding excipients and the like; when prepared into a syrup, preparation can be carried out by adding sweeteners and the like; and while when prepared into an emulsion or a suspension, preparation can be carried out by adding suspending agents, surfactants, emulsifying agents and the like.

Examples of the excipient include lactose, white sugar, glucose, starch, sucrose, microcrystalline cellulose, powdered licorice, mannitol, sodium hydrogen carbonate, calcium phosphate, calcium sulfate and the like.

Examples of the binding agent include a 5 to 10 wt % starch liquid paste, a 10 to 20 wt % gum arabic solution or gelatin solution, a 1 to 5 wt % tragacanth solution, a carboxymethylcellulose solution, a sodium alginate solution, glycerin and the like.

Examples of the disintegrant include starch, calcium carbonate and the like.

Examples of the lubricant include magnesium stearate, stearic acid, calcium stearate, purified talc and the like.

Examples of the sweetener include glucose, fructose, invert sugar, sorbitol, xylitol, glycerin, simple syrup and the like.

Examples of the surfactant include sodium lauryl sulfate, Polysorbate 80, sorbitan monofatty acid ester, Polyoxyl 40 stearate and the like.

Examples of the suspending agent include gum arabic, sodium alginate, carboxymethylcellulose sodium, methylcellulose, bentonite and the like

Examples of the emulsifying agent include gum arabic, tragacanth, gelatin, Polysorbate 80 and the like.

In addition, when the compound (I) or a salt thereof

is prepared into the formulations, if desired, appropriate amounts of colorants, preservatives, fragrance, flavoring agents, stabilizers, thickening agents and the like that are conventionally used in the art of purification can be suitably added.

The preparation of the present invention, which contains the compound (I) or a salt thereof, can be used safely with stability and low toxicity. Daily dose of the preparation may vary depending on the condition or body weight of the patient, kind of compound, administration route and the like. However, for example, when the preparation is to be orally administered to a patient having thrombosis, the daily dose for adult (body weight about 60 kg) is from about 1 to 2,000 mg, preferably from about 3 to 1,000 mg, and more preferably from about 10 to 500 mg, in terms of an effective ingredient (the compound represented by the formula (I) or a salt thereof), which can be administered all at once, or in 2 to 3 portions.

When the compound (I) or a salt thereof of the present invention is to be parenterally administered, it is usually administered in the form of liquid formulation (for example, injectable preparation). Daily dose thereof may vary depending on the subject of administration, subject organ, symptoms, administration method and the like. However, the preparation is favorably administered, for example, in the

form of injectable preparation in an amount of usually from about 0.01 mg to about 100 mg, preferably from about 0.01 to about 50 mg, and more preferably from about 0.01 to about 20 mg, per 1 kg of body weight, through intravenous injection. The injectable preparation includes, in addition to intravenous injectable preparation, subcutaneous injectable preparation, intradermal injectable preparation, muscular injectable preparation, drip infusion preparation and the like, while the sustained preparation includes iontophoretic transdermal preparation and the like. Such injectable preparations are prepared by methods known per se, that is, by dissolving, suspending or emulsifying the compound (I) or a salt thereof of the present invention in sterile aqueous liquid or oily liquid. Examples of the aqueous liquid for injection include physiological saline, isotonic solutions containing glucose or other pharmaceutical adjuvants (e.g, D-sorbitol, D-mannitol, sodium chloride, etc.) and the like, and these may be used in combination with appropriate dissolution aids, for example, alcohol (e.g., ethanol), polyalcohol (e.g., propylene glycol, polyethylene glycol), nonionic surfactant (e.g., Polysorbate 80, HCO-50) and the like. Examples of the oily liquid include sesame oil, soybean oil and the like, and these may be used in combination with dissolution aids such as benzyl benzoate, benzyl alcohol and the like.

Furthermore, buffering agents (e.g., phosphate buffer solution, sodium acetate buffer solution), soothing agents (e.g., benzalkonium chloride, procaine chloride, etc.), stabilizers (e.g., human serum albumin, polyethylene glycol, etc.), preservatives (e.g., benzyl alcohol, phenol, etc.) and the like may be mixed therewith. Prepared injection liquids are usually filled in ampoules.

The compound of the present invention can be used in combination with drugs (hereinafter, abbreviated to combination drugs) such as thrombolytic agents (e.g., TPA, urokinase, etc.), Alzheimer's drugs (e.g., Calan, etc.), cholesterol treating drugs (e.g., HMG-CoA reductase inhibitor such as simvastatin or pravastatin, etc.), TG lower drugs (e.g., Clofibrat, etc.), AII antagonists (e.g., candesartan, cilexetil, losartan, etc.), antiplatelet drugs (e.g., clopidogrel, abciximab, aspirin, etc.), Ca antagonists (e.g., calslot, amlodipine, etc.), ACE inhibitors (e.g., enalapril, captopril, etc.), β-blocking drugs (e.g., metoprolol, carvedilol, etc.), antiarrhythmic drugs (e.g., procaine amide, etc.) and the like. These combination drugs may be low molecular weight compounds, or may be proteins of high molecular weight, polypeptides, antibodies, vaccines or the like. Here, the administration form of the compound of the present invention and the combination drugs is not particularly limited, and it is

favorable that the compound of the present invention and the combination drugs are in a combined state upon administration. For such administration form, for example, mention may be made of (1) administration of a single preparation obtained by simultaneously formulating the compound of the present invention and the combination drug, (2) simultaneous administration through the same administration route of two preparations obtained by separately formulating the compound of the present invention and the combination drug, (3) administration with a time interval through the same administration route of two preparations obtained by separately formulating the compound of the present invention and the combination drug, (4) simultaneous administration through different administration routes of two preparations obtained by separately formulating the compound of the present invention and the combination drug, (5) administration with a time interval through different administration routes of two preparations obtained by separately formulating the compound of the present invention and the combination drug (e.g., administration in order of the compound of the present invention → combination drug, or administration in the reverse order), or the like. The amount of the combination drug to be administered can be appropriately selected with reference to the clinically used dosage. The

mixing ratio of the compound of the present invention and the combination drug can be appropriately selected in accordance with the subject of administration, administration route, disease to be treated, symptoms, combination, and the like. For example, when the subject of administration is human, the combination drug may be used in an amount of 0.01 to 100 parts by weight based on 1 part by weight of the compound of the present invention.

The present invention is further described in detail with reference to Examples, Preparation Examples and Experimental Examples, but they are merely illustrations and are not intended to limit the present invention and may be modified in a range not to be departing from the scope of the present invention.

The elution in column chromatography of examples was carried out under observation by means of TLC (Thin Layer Chromatography). In the TLC observation, 60F254 (manufactured by Merck & Co., Inc.) or NH (manufactured by Fuji Silysia Chemical Ltd.) were adopted as a TLC plate, the solvent used for the elution in column chromatography was adopted as an eluent, a UV detector was adopted as the means for detection. As the silica gel for column, Kieselgel 60 (70 to 230 meshes) or Kieselgel 60 (230 to 400 meshes), manufactured by the same Merck & Co., Inc., was

used. As the basic silica gel for column, NH-DM 1020 (manufactured by Fuji Silysia Chemical, Ltd.; 100 to 200 mesh) was used. NMR spectra were measured with a Varian Gemini 200 or 300 spectrometer by using tetramethylsilane as internal or external standard. The chemical shift was indicated by δ, and the coupling constant was indicated by Hz. IR spectra were measured with a Shimadzu FTZR-8200 spectrometer. The numeric value in parenthesis with regard to a mixed solvent is a volumetric mixing ratio of each solvent. Moreover, "%" in the solution represents the number of grams in 100 mL of a solution. Abbreviations employed in examples are described below.

s: singlet

d: doublet

t: triplet

q: quartet

dd: double doublet

m: multiplet

br: broad

brs: broad singlet

J: coupling constant

WSC: water-soluble carbodiimides

THF: tetrahydrofuran

DMF: N,N'-dimethylformamide

DMSO: diemthylsulfoxide

HOBt: 1-hydroxybenztriazole

Example 1

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine hydrochloride

1a) 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine

5-Chloroimidazo[1,2-a]pyridine (4.58 g) and piperazine (25.8 g) were mixed, and stirred at 125°C for 18 hours under argon atmosphere. To the resulting solid were added water (200 mL) and chloroform (200 mL), and the organic layer was separated. The organic layer was washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate and then solvent was distilled away under reduced pressure. The obtained residue was dissolved in ethanol (100 mL), di-tert-butyl dicarbonate (6.55 g) was added dropwise at room temperature thereto, and the reaction solution was stirred at room temperature for 1 hour. The solvent was distilled away under reduced pressure, water (200 mL) was added to the residue, and extracted with ethyl acetate (200 mL). The extract was washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate and then solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 10:1) to give

the title compound 8.39 g (yield 93%) as a pale yellow solid.

NMR ($CDCl_3$) δ 1.50 (9H, s), 3.06-3.11 (4H, m), 3.54-3.82 (4H, m), 6.30 (1H, d, J = 7.2 Hz), 7.18 (1H, dd, J = 9.2, 7.2 Hz), 7.42 (1H, d, J = 8.8 Hz), 7.57 (1H, s), 7.66 (1H, s).

1b) 5-(Piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine (8.39 g) obtained in Example 1a) was added to concentrated hydrochloric acid (22.8 mL), and stirred at room temperature for 20 minutes. To the reaction solution was added ethanol (85 mL), the resulting mixture was concentrated under reduced pressure, and the precipitated crystals were collected by filtration. The crystals were washed with ethanol (10 mL) and diethyl ether (10 mL), then dried under reduced pressure to give the title compound 5.24 g (yield 69%) as white crystals.

NMR (D_2O) δ 3.59-3.61 (4H, m), 3.61-3.66 (4H, m), 7.15 (1H, d, J = 7.8 Hz), 7.70 (1H, d, J = 9.2 Hz), 7.92-8.00 (2H, m), 8.06 (1H, s).

1c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine

To a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.75 g) and HOBt·H_2O (0.57 g) in acetonitrile (15 mL) was added WSC (0.72 g),

and stirred at room temperature for 20 minutes. To the reaction mixture was added dropwise at room temperature a solution of 5-(Piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (0.83 g) obtained in Example 1b), triethylamine (1.1 mL) and DBU (0.9mL) in acetonitrile (10 mL), and the reaction solution was stirred at room temperature for 3 hours. The solvent was distilled away under reduced pressure, water (50 mL) was added to the residue, and extracted with chloroform (50 mL). The extract was washed with saturated saline (50 mL), dried over anhydrous magnesium sulfate and then solvent was distilled away under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 5:1) to give the title compound 1.09 g (yield 91%) as a pale yellow powder.
NMR ($CDCl_3$) δ 2.96 (2H, t, J = 3.6 Hz), 3.00-3.22 (4H, m), 3.61 (2H, t, J = 4.0 Hz), 3.65-3.92 (4H, m), 6.28 (1H, d, J = 6.9 Hz), 7.19 (1H, dd, J = 9.0, 6.9 Hz), 7.44 (1H, d, J = 9.0 Hz), 7.55 (1H, s), 7.60 (1H, d, J = 8.7 Hz), 7.67 (1H, s), 7.91-7.96 (4H, m), 8.50 (1H, br).

1d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine hydrochloride

To a solution of 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine (1.3 g) obtained in Example 1c) in ethanol (15

mL) was added concentrated hydrochloric acid (0.44 mL) at room temperature. The obtained mixture was concentrated under reduced pressure, ethanol-diethyl ether was added to the residue, and the deposited precipitate was collected by filtration. The precipitate was washed with ether (10 mL), and dried under reduced pressure to give the title compound 1.22 g (yield 87%) as white powder.

NMR (DMSO-d_6) δ 2.83 (2H, t, J = 7.4 Hz), 2.94-3.08 (2H, m), 3.08-3.20 (2H, m), 3.48-3.84 (6H, m), 6.98 (1H, d, J = 7.4 Hz), 7.68-7.76 (2H, m), 7.90-8.04 (2H, m), 8.18-8.24 (2H, m), 8.24-8.32 (3H, m), 8.68 (1H, br), LC/MS 483 (M-HCl).

Example 2

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine hydrochloride

2a) 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

5-Chloro-2-methylimidazo[1,2-a]pyridine (5.00 g) and piperazine (25.8 g) were mixed, and stirred at 125°C for 18 hours under argon atmosphere. To the resulting solid were added water (200 mL) and chloroform (200 mL), and the organic layer was separated. The organic layer was washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate and then solvent was distilled away under reduced pressure. The obtained residue was dissolved in ethanol (100 mL), di-tert-butyl dicarbonate (6.55 g) was

added dropwise at room temperature thereto, and the reaction solution was stirred at room temperature for 1 hour. The solvent was distilled away under reduced pressure, water (200 mL) was added to the residue, and extracted with ethyl acetate (200 mL). The extract was washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate and then solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 10:1) to give the title compound 8.46 g (yield 89%) as a pale yellow solid.

NMR ($CDCl_3$) δ 1.50 (9H, s), 2.48 (3H, s), 2.97-3.15 (4H, m), 3.58-3.78 (4H, m), 6.23 (1H, d, J = 8.2 Hz), 7.13 (1H, dd, J = 8.8, 7.0 Hz), 7.28-7.35 (2H, m).

2b) 5-(1-Piperazinyl)-2-methylimidazo[1,2-a]pyridine dihydrochloride

5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (8.46 g) obtained in Example 2a) was added to concentrated hydrochloric acid (22.0 mL), and stirred at room temperature for 20 minutes. To the reaction solution was added ethanol (90 mL), the resulting mixture was concentrated under reduced pressure, and the precipitated crystals were collected by filtration. The crystals were washed with ethanol (10 mL) and diethyl ether (10 mL), then dried under reduced pressure to give the

title compound 6.28 g (yield 81%) as pale yellow crystals.
NMR (D_2O) δ 2.59 (3H, s), 3.48-3.61 (4H, m), 3.61-3.72 (4H, m), 7.11 (1H, d, J = 7.8 Hz), 7.61 (1H, d, J = 9.0 Hz), 7.80 (1H, s), 7.91 (1H, dd, J = 8.8, 7.8 Hz).

2c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.16 g (93%) was obtained from 5-(1-piperazinyl)-2-methylimidazo[1,2-a]pyridine dihydrochloride (0.87 g) obtained in Example 2b).
NMR ($CDCl_3$) δ 2.48 (3H, s), 2.89-3.18 (6H, m), 3.60 (2H, m), 3.66-.90 (4H, m), 6.22 (1H, d, J = 4.8 Hz), 7.14 (1H, dd, J = 5.8, 4.8 Hz), 7.28 (1H, s), 7.33 (1H, d, J = 5.2 Hz), 7.59-7.62 (1H, m), 7.88-8.01 (4H, m), 8.49 (1H, br).

2d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 1d), the title compound 1.24 g (87%) was obtained as a white powder from 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (1.33 g) obtained in Example 2c).
NMR (DMSO-d_6) δ 2.52 (3H, s), 2.84 (2H, t, J = 7.4 Hz), 2.94-3.08 (2H, m), 3.08-3.23 (2H, m), 3.23-3.54 (2H, m), 3.54-3.78 (4H, m), 6.93 (1H, d, 7.2 Hz), 7.60 (1H, d, 8.8 Hz), 7.71-7.76 (1H, m), 7.88 (1H, dd, J = 8.8, 8.0 Hz),

7.99 (1H, s), 8.03-8.04 (1H, m), 8.18-8.32 (3H, m), 8.68 (1H, br), LC/MS 497 (M-HCl).

Example 3

5-[4-[3-[(1-tert-Butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine

3a) tert-Butyl 3-[(5-chloro-2-indolyl)thio]propionate

5-Chlorooxyindole (25.8 g) and Lawesson's reagent (93.5 g) were added to pyridine (300 mL), and the mixture was refluxed for 16 hours. The reaction solution was poured into ice-water (2 L), and allowed to stand at room temperature for 18 hours. The precipitated solid was collected by filtration, washed with water (100 mL), and dried. To a suspension of the obtained yellow solid in acetonitrile (200 mL) were added tert-butyl acrylate (22.6 mL) and triethylamine (21.5 mL), and refluxed for 1 hour. The solvent was distilled away under reduced pressure, water (150 mL) was added to the residue, and extracted with ethyl acetate (150 mL). The extract was washed with saturated saline (150 mL), dried over anhydrous magnesium sulfate and then solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexane 1:4) to give the title compound 24.1 g (yield 50%) as a pale yellow solid.

NMR ($CDCl_3$) δ 1.47 (9H, s), 2.55 (2H, t, J = 6.9 Hz), 3.03 (2H, t, J = 6.9 Hz), 6.58-6.59 (1H, m), 7.12-7.15 (1H, m), 7.24-7.27 (1H, m), 7.51-7.52 (1H, m), 8.73 (1H, br).

3b) tert-Butyl 3-[(5-chloro-2-indolyl)sulfonyl]propionate

To a solution of tert-butyl 3-[(5-chloro-2-indolyl)thio]propionate (1.56 g) obtained in Example 3a) in dichloromethane (15 mL) was added 70% 3-chloroperbenzoic acid (3.08 g) at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction solution was diluted with dichloromethane (50 mL), and washed sequentially with saturated aqueous sodium thiosulfate solution (50 mL), saturated aqueous sodium hydrogen carbonate solution (50 mL) and saturated saline (50 mL). The organic layer was dried over anhydrous magnesium sulfate, and solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexane 1:4) to give the title compound 1.58 g (yield 92%) as a white solid.

NMR ($CDCl_3$) δ 1.38 (9H, s), 2.72 (2H, t, J = 7.4 Hz), 3.56 (2H, t, J = 7.4 Hz), 7.13-7.14 (1H, m), 7.30-7.36 (1H, m), 7.40-7.44 (1H, m), 7.68-7.69 (1H, m), 9.52 (1H, br).

3c) Allyl 3-[(1-tert-butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionate

To a solution of tert-butyl 3-[(5-chloro-2-indolyl)sulfonyl]propionate (13.8 g) obtained in Example

3b) in acetic acid (250 mL) was added concentrated hydrochloric acid (33 mL) at room temperature, and stirred at 60°C for 1 hour. The solid obtained by removing the solvent under reduced pressure was dissolved in DMF (100 mL), and triethylamine (6.7 mL) and allyl bromide (10.4 mL) were added thereto, followed by stirring at 60°C for 2 hours. The reaction solution was poured into ice-water (500 mL), and extracted with ethyl acetate (150 mL). The extract was washed with water (150 mL x 3) and saturated saline (100 mL), dried over anhydrous magnesium sulfate, and solvent was distilled away under reduced pressure. To a solution of the obtained solid and 4-dimethylaminopyridine (4.89 g) in acetonitrile (150 mL) was added dropwise di-tert-butyl dicarbonate (8.73 g) at room temperature, and stirred at room temperature for 1 hour. The solvent was distilled away under reduced pressure, water (150 mL) was added to the residue, and extracted with ethyl acetate (150 mL). The extract was washed with saturated saline (150 mL), dried over anhydrous magnesium sulfate, then solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexane 1:4) to give the title compound 10.6 g (yield 62%) as a pale brown solid. NMR ($CDCl_3$) δ 1.74 (9H, s), 2.90 (2H, t, J = 7.4 Hz), 4.03 (2H, t, J = 7.4 Hz), 4.47-4.52 (2H, m), 5.17-5.30 (2H, m),

5.72-5.93 (1H, m), 7.42-7.53 (2H, m), 7.64-7.65 (1H, m), 7.98 (1H, d, J = 9.2 Hz).

3d) 3-[(1-tert-Butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionic acid

To a solution of allyl 3-[(1-tert-butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionate (4.27 g) obtained in Example 3c) in THF (40 mL) was added Meldrum's acid (2.16 g), then added palladium(0)tetrakistriphenylphosphine (0.58 g), and stirred at room temperature for 3 hours under argon atmosphere. The solvent was distilled away under reduced pressure, 1N hydrochloric acid (50 mL) was added to the residue, and extracted with ethyl acetate (50 mL). The extract was dried over anhydrous magnesium sulfate, solvent was distilled away under reduced pressure, then diisopropyl ether was added to the residue, and the resulting precipitate was collected by filtration. The precipitate was washed with diisopropyl ether (5 mL), and dried under reduced pressure to give the title compound 3.29 g (yield 85%) as a pale brown solid.

NMR (DMSO-d_6) δ 1.68 (9H, s), 2.71 (2H, t, J = 7.0 Hz), 3.96 (2H, t, J = 7.0 Hz), 7.57-7.62 (2H, m), 7.93-7.94 (1H, m), 8.05 (1H, d, J = 9.2 Hz).

3e) 5-[4-[3-[(1-tert-Butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine

To a solution of 3-[(1-tert-butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionic acid (0.97 g) obtained in Example 3d) and HOBt·H_2O (0.57 g) in acetonitrile (15 mL) was added WSC (0.72 g), and stirred at room temperature for 20 minutes. To the resulting reaction mixture was added dropwise a solution of 5-(piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (0.83 g), triethylamine (1.05 mL) and DBU (0.9 mL) in acetonitrile (10 mL) at room temperature, and stirred at room temperature for 3 hours. The solvent was distilled away under reduced pressure, water (50 mL) was added to the residue, and extracted with chloroform (50 mL). The extract was washed with saturated saline (50 mL), dried over anhydrous magnesium sulfate, and solvent was distilled away under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 5:1) to give the title compound 1.09 g (yield 76%) as a pale yellow powder.

NMR ($CDCl_3$) δ 1.74 (9H, s), 2.84-3.20 (4H, m), 3.20-3.52 (2H, m), 3.52-3.93 (4H, m), 4.14 (2H, t, J = 7.0 Hz), 6.25-6.33 (1H, m), 7.08-7.35 (2H, m), 7.35-7.58 (3H, m), 7.59-7.72 (2H, m), 7.88-8.02 (1H, m), LC/MS 572 (M).

Example 4

5-[4-[3-[(5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine hydrochloride

5-[4-[3-[(1-tert-Butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine (1.00 g) obtained in Example 3e) was dissolved in concentrated hydrochloric acid (2.9 mL), and stirred at room temperature for 20 minutes. To the reaction solution was added ethanol (25 mL), and concentrated under reduced pressure. To the residue was added ethanol-ether, and the resulted precipitate was collected by filtration. The precipitate was dried under reduced pressure to give the title compound 0.75 g (yield 85%) as a white powder.

NMR (DMSO-d_6) δ 2.84 (2H, t, J = 7.2 Hz), 2.93-3.08 (2H, m), 3.08-3.24 (2H, m), 3.24-3.57 (2H, m), 3.57-3.79 (4H, m), 7.01 (1H, d, J = 7.0 Hz), 7.17-7.18 (1H, m), 7.32-7.37 (1H, m), 7.55 (1H, d, J = 8.6 Hz), 7.69 (1H, d, J = 8.8 Hz), 7.81-7.82 (1H, m), 7.94 (1H, dd, J = 8.8, 7.8 Hz), 8.20-8.21 (1H, m), 8.28-8.30 (1H, m), LC/MS 472 (M-HCl).

Example 5

5-[4-[3-[(1-tert-Butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 3e), the title compound 1.03 g (70%) was obtained as a pale yellow powder by using 2-methyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (0.87 g).

NMR ($CDCl_3$) δ 1.75 (9H, s), 2.48 (3H, s), 2.87-3.19 (6H, m),

3.60 (4H, m), 4.11 (2H, t, J = 8.0 Hz), 6.23 (1H, d, J = 7.4 Hz), 7.10-7.18 (1H, m), 7.26-7.35 (2H, m), 7.40-7.53 (2H, m), 7.65-7.70 (1H, m), 8.00 (1H, d, J = 9.2 Hz), LC/MS 586 (M).

Example 6

5-[4-[3-[(5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 4, the title compound 0.47 g (73%) was obtained as a white powder from 5-[4-[3-[(1-tert-butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.72 g) obtained in Example 5. NMR (DMSO-d_6) δ 2.51 (3H, s), 2.84 (2H, t, J = 7.2 Hz), 2.92-3.07 (2H, m), 3.07-3.23 (2H, m), 3.23-3.54 (2H, m), 3.54-3.80 (4H, m), 6.96 (1H, m), 7.17-7.18 (1H, m), 7.32-7.37 (1H, m), 7.52-7.62 (2H, m), 7.81-7.93 (2H, m), 7.99 (1H, s), LC/MS 486 (M-HCl).

Example 7

5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-ethoxycarbonyl-1-piperazinyl]imidazo[1,2-a]pyridine

7a) Ethyl 4-(imidazo[1,2-a]pyridin-5-yl)-2-piperazinecarboxylate

5-Fluoroimidazopyridine (Ikemoto et al., Tetrahedron, 2002, Vol. 58, p. 489) (1.05 g) and ethyl 2-piperazinecarboxylate were mixed, and stirred at 100°C for

5 hours. The reaction mixture was diluted with chloroform and aqueous sodium hydrogen carbonate solution, and the organic layer was separated. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol 10:1) to give the title compound 1.4 g (yield 66%) as a brown oil. NMR ($CDCl_3$) δ1.23-1.34 (3H, m), 2.20-3.82 (8H, m), 4.14-4.31 (2H, m), 6.33 (1H, dd, J = 0.9 and 7.2 Hz), 7.15-7.71 (4H, m).

7b) 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-ethoxycarbonyl-1-piperazinyl]imidazo[1,2-a]pyridine

To a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoic acid (0.76 g) and HOBt (0.59 g) in acetonitrile (15 mL) was added WSC (0.73 g), and stirred at room temperature for 15 minutes. To the reaction mixture was added a solution of ethyl 4-(imidazo[1,2-a]pyridin-5-yl)-2-piperazinecarboxylate (0.70 g) and triethylamine (0.78 mL) in acetonitrile at room temperature, and stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure, then diluted with aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica

gel column chromatography (eluent: ethyl acetate) to give the title compound 0.26 g (yield 18%) as a colorless powder.

NMR ($CDCl_3$) δ1.24-1.34 (3H, m), 2.75-5.30 (13H, m), 6.29-6.34 (1H, m), 7.19 (1H, dd, J = 7.5 and 9.0 Hz), 7.40-7.47 (1H, m), 7.58-7.97 (7H, m), 8.48-8.49 (1H, m).

Elemental analysis for $C_{27}H_{27}ClN_4O_5S \cdot 0.3H_2O$

Calcd (%): C, 57.86; H, 4.96; N, 10.00

Found (%): C, 57.80; H, 5.07; N, 10.33.

Example 8

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-carbamoyl-1-piperazinyl]imidazo[1,2-a]pyridine

To a solution of 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-carboxy-1-piperazinyl]imidazo[1,2-a]pyridine (0.30 g) obtained in Example 10, HOBt-NH_3 complex (0.16 g) and WSC (0.15 g) in DMF (10 mL) was added triethylamine (0.3 g), and stirred at room temperature for 40 hours. The reaction mixture was concentrated under reduced pressure, then diluted with aqueous sodium hydrogen carbonate solution, and extracted with mixed solvent of ethyl acetate and THF. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 20:1), and recrystallized from ethyl acetate-diethyl ether to give the title compound 100 mg

(yield 36%) as a white powder.

NMR ($CDCl_3$) δ2.50 (3H, s), 2.54-5.80 (12H, m), 6.22 (1H, d, J = 6.6 Hz), 6.79 (1H, br), 7.10 (1H, dd, 7.0 and 9.0 Hz), 7.33 (1H, d, J = 9.2 Hz), 7.62 (1H, dd, J = 8.8 and 2.0 Hz), 7.85-8.00 (4H, m), 8.08 (1H, s), 8.49 (1H, s).

Elemental analysis for $C_{25}H_{24}ClN_5O_4S \cdot 0.5H_2O$

Calcd (%): C, 56.12 ; H, 4.71 ; N, 13.09

Found (%): C, 56.14 ; H, 4.94 ; N, 12.97.

Example 9

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-tert-butoxycarbonyl-1-piperazinyl]imidazo[1,2-a]pyridine

9a) tert-Butyl 4-(imidazo[1,2-a]pyridin-5-yl)-2-piperazinecarboxylate

According to a similar manner to Example 7a), the title compound 0.65 g (72%) was obtained as a brown oil from tert-butyl 2-piperazinecarboxylate (1.68 g).

NMR ($CDCl_3$) δ 1.50 (9H, s), 2.20-3.80 (8H, m), 6.32 (1H, d, J = 6.3 Hz), 7.17 (1H, dd, J = 9.0 and 7.2 Hz), 7.41 (1H, d, J = 9.0 Hz), 7.64 (1H, d, J = 1.5 Hz), 7.17 (1H, s).

9b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-tert-butoxycarbonyl-1-piperazinyl]imidazo[1,2-a]pyridine

According to a similar manner to Example 7b), the title compound 0.47 g (38%) was obtained as a colorless powder from tert-butyl 4-(imidazo[1,2-a]pyridin-5-yl)-2-piperazinecarboxylate (0.65 g) obtained in Example 9a).

NMR ($CDCl_3$) δ1.46 (9H, s), 2.75-5.19 (11H, m), 6.29 (1H, d, J = 7.2 Hz), 7.19 (1H, dt, J = 7.2 and 9.2 Hz), 7.45 (1H, d, J = 8.7 Hz), 7.58-7.97 (7H, m), 8.49 (1H, d, J = 0.6 Hz).

Elemental analysis for $C_{29}H_{31}ClN_4O_5S \cdot 0.7H_2O$

Calcd (%): C, 58.47; H, 5.48; N, 9.40

Found (%): C, 58.39; H, 5.75; N, 9.30.

Example 10

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-carboxy-1-piperazinyl]imidazo[1,2-a]pyridine

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-tert-butoxycarbonyl-1-piperazinyl]imidazo[1,2-a]pyridine (0.20 g) obtained in Example 9 was dissolved in concentrated hydrochloric acid (3 mL), and stirred at room temperature for 3 hours. The hydrochloric acid was distilled away under reduced pressure to give the title compound 0.20 g (quantitative) as a colorless powder.

NMR (DMSO-d_6) δ2.50-4.29 (10H, m), 5.12 (1H, d, J = 10.5 Hz), 7.01 (1H, d, J = 6.9 Hz), 7.69-7.76 (2H, m), 7.92 (1H, dd, J = 8.1 and 9.0 Hz), 8.03 (1H, t, J = 7.2 Hz), 8.19-8.35 (5H, m), 8.68 (1H, d, J = 8.7 Hz).

Elemental analysis for $C_{25}H_{24}Cl_2N_4O_5S \cdot 0.3MeCN \cdot H_2O$

Calcd (%): C, 51.78; H, 4.57; N, 10.14

Found (%): C, 51.93; H, 4.83; N, 10.40.

Example 11

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-methyl-

1-piperazinyl]imidazo[1,2-a]pyridine hydrochloride

11a) 5-[4-(tert-Butoxycarbonyl)-3-methyl-1-piperazinyl]imidazo[1,2-a]pyridine

5-chloroimidazo[1,2-a]pyridine (4.58 g) and 2-methylpiperazine (30.1 g) are mixed, and stirred at 125°C for 18 hours under argon atmosphere. The solid obtained by cooling was dissolved in water (200 mL) and chloroform (200 mL), and the organic layer was washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate, and then solvent was distilled away under reduced pressure. The obtained residue was dissolved in ethanol (100 mL), and di-tert-butyl dicarbonate (6.55 g) was added dropwise at room temperature, and the reaction solution was stirred at room temperature for 1 hour. The solvent was distilled away under reduced pressure, water (200 mL) was added to the residue, and extracted with ethyl acetate (200 mL). The extract was washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate, and then solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 10:1) to give the title compound 8.54 g (yield 90%) as a pale yellow powder.

NMR ($CDCl_3$) δ 1.47-1.51 (12H, s), 2.71-2.97 (2H, m), 3.22-3.45 (3H, m), 3.98-4.13 (1H, m), 4.37-4.54 (1H, m), 6.29 (1H, d, J = 7.4 Hz), 7.18 (1H, dd, J = 8.8, 7.0 Hz), 7.42

(1H, d, J = 8.8 Hz), 7.64-7.66 (2H, m).

11b) 5-(3-Methyl-1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

5-[4-(tert-Butoxycarbonyl)-3-methyl-1-piperazinyl]imidazo[1,2-a]pyridine (8.54 g) obtained in Example 11a) was added to concentrated hydrochloric acid (22.2 mL), and stirred at room temperature for 20 minutes. To the reaction solution was added ethanol (85 mL), and the resulting mixture was concentrated under reduced pressure, then the precipitated crystals were collected by filtration. The crystals were washed with ethanol (10 mL) and diethyl ether (10 mL), and dried under reduced pressure to give the title compound 5.93 g (yield 76%) as pale brown crystals. NMR (D_2O) δ 1.50 (3H, d, J = 6.6 Hz), 3.14-3.28 (1H, m), 3.31-3.48 (1H, m), 3.53-3.81 (4H, m), 3.81-3.98 (1H, m), 7.16 (1H, d, J = 7.6 Hz), 7.71 (1H, d, J = 8.8 Hz), 7.93-8.02 (2H, m), 8.06-8.08 (1H, m).

11c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-methyl-1-piperazinyl]imidazo[1,2-a]pyridine

To a solution of 3-[(6-Chloro-2-naphthyl)sulfonyl]propionic acid (1.49 g) and HOBt·H_2O (0.77 g) in acetonitrile (15 mL) was added WSC (0.48 g), and stirred at room temperature for 20 minutes. To the resulting reaction mixture was added dropwise a solution of 5-(3-methyl-1-piperazinyl)imidazo[1,2-a]pyridine

dihydrochloride (0.87 g) obtained in Example 11b), triethylamine (1.4 mL) and DBU (0.9 mL) in acetonitrile (10 mL) at room temperature, and stirred at room temperature for 6 hours. The solvent was distilled away under reduced pressure, water (50 mL) was added to the residue, and extracted with chloroform (50 mL). The extract was washed with saturated saline (50 mL), dried over anhydrous magnesium sulfate, and solvent was distilled away under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 5:1) to give the title compound 1.06 g (yield 71%) as a white powder.

NMR ($CDCl_3$) δ 1.36-1.69 (3H, m), 2.48-3.17 (4H, m), 3.17-3.48 (3H, m), 3.48-3.72 (2H, m), 3.72-3.94 (0.5H, m), 4.17-4.34 (0.5H, m), 4.44-4.68 (0.5H, m), 4.77-4.98 (0.5H, m), 6.27 (1H, d, J = 7.4 Hz), 7.19 (1H, dd, J = 8.8, 6.8 Hz), 7.45 (1H, d, J = 8.8 Hz), 7.58-7.68 (3H, m), 7.91-7.98 (4H, m), 8.50 (1H, br).

11d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-methyl-1-piperazinyl]imidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 1d), the title compound 0.47 g (93%) was obtained as a colorless powder from 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-methyl-1-piperazinyl]imidazo[1,2-a]pyridine (0.47 g) obtained in

Example 11c).

NMR (DMSO-d_6) δ 1.12-1.48 (3H, m), 2.58-3.04 (3H, m), 3.04-3.31 (2H, m), 3.31-3.63 (2H, m), 3.63-3.93 (2.5H, m), 4.09-4.41 (1H, m), 4.51-4.72 (0.5H, m), 6.98 (1H, d, J = 6.8 Hz), 7.68-7.77 (2H, m), 7.90-8.04 (2H, m), 8.15-8.32 (5H, m), 8.68 (1H, br), LC/MS 498 (M-HCl).

Example 12

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-methyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine hydrochloride

12a) 5-[4-(tert-Butoxycarbonyl)-3-methyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

5-chloro-2-methylimidazo[1,2-a]pyridine (5.00 g) and 2-methylpiperazine (30.1 g) were mixed, and stirred at 125°C for 36 hours under argon atmosphere. The solid obtained by cooling was dissolved in water (200 mL) and chloroform (200 mL), and the organic layer was separated. The organic layer was washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate, and solvent was distilled away under reduced pressure. The obtained residue was dissolved in ethanol (100 mL), and di-tert-butyl dicarbonate (6.55 g) was added dropwise at room temperature, and the reaction solution was stirred at room temperature for 1 hour. The solvent was distilled away under reduced pressure, water (200 mL) was added to the residue, and extracted with ethyl acetate (200 mL). The

extract was washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate, and then solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 10:1) to give the title compound 8.62 g (yield 93%) as a pale yellow powder.

NMR ($CDCl_3$) δ 1.46-1.50 (12H, m), 2.48 (3H, s), 2.71-2.79 (1H, m), 2.86-2.91 (1H, m), 3.23-3.42 (3H, m), 3.98-4.12 (1H, m), 4.37-4.51 (1H, m), 6.22 (1H, d, J = 7.2 Hz), 7.08-7.15 (1H, m), 7.27-7.35 (2H, m).

12b) 2-Methyl-5-(3-methyl-1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

5-[4-(tert-Butoxycarbonyl)-3-methyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (8.62 g) obtained in Example 12a) was added to concentrated hydrochloric acid (21.4 mL), and stirred at room temperature for 20 minutes. To the reaction solution was added ethanol (85 mL), and the resulting mixture was concentrated under reduced pressure, then the precipitated crystals were collected by filtration. The crystals were washed with ethanol (10 mL) and diethyl ether (10 mL), and dried under reduced pressure to give the title compound 6.33 g (yield 80%) as pale brown crystals.

NMR (D_2O) δ 1.48 (3H, d, J = 6.6 Hz), 2.58 (3H, s), 3.08-3.20 (1H, m), 3.23-3.43 (1H, m), 3.49-3.77 (4H, m), 3.77-3.93 (1H, m), 7.09 (1H, d, J = 7.6 Hz), 7.59 (1H, d, J =

8.8 Hz), 7.77 (1H, s), 7.89 (1H, dd, J = 8.8, 8.0 Hz).

12c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-methyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 11c), the title compound 1.01 g (66%) was obtained as a pale brown powder from 2-methyl-5-(3-methyl-1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (0.91 g) obtained in Example 12b).

NMR ($CDCl_3$) δ 1.41-1.65 (3H, m), 2.48 (3H, s), 2.67-3.01 (3H, m), 3.01-3.17 (1H, m), 3.17-3.48 (3H, m), 3.48-3.93 (2.5H, m), 4.13-4.34 (0.5H, m), 4.43-4.58 (0.5H, m), 4.77-4.97 (0.5H, m), 6.22 (1H, d, J = 7.4 Hz), 7.14 (1H, dd, J = 8.8, 7.0 Hz), 7.31-7.35 (2H, m), 7.52-7.68 (1H, m), 7.90-7.98 (4H, m), 8.49 (1H, br).

12d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-methyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 1d), the title compound 0.51 g (98%) was obtained as a white powder from 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-methyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.61 g) obtained in Example 12c).

NMR (DMSO-d_6) δ 1.09-1.43 (3H, m), 2.51 (3H, s), 2.56-3.04 (3H, m), 3.04-3.36 (2H, m), 3.36-3.61 (2H, m), 3.61-3.90 (2.5H, m), 4.11-4.42 (1H, m), 4.48-4.69 (0.5H, m), 6.93 (1H,

d, J = 7.4 Hz), 7.61 (1H, d, J = 8.4 Hz), 7.74 (1H, dd, J = 8.6, 2.0 Hz), 7.84-8.04 (3H, m), 8.16-8.27 (3H, m), 8.67 (1H, br), LC/MS 511 (M-HCl).

Example 13

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine

13a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine

5-chloro-2-ethoxycarbonylimidazo[1,2-a]pyridine (12.0 g) and piperazine (46.0 g) were added to acetonitrile (200 mL), and refluxed for 72 hours under argon atmosphere. The solvent was distilled away under reduced pressure, and to the residue was added water (250 mL), and extracted with chloroform (250 mL). The extract was washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate, and solvent was distilled away under reduced pressure. The residue was dissolved in ethanol (150 mL), and di-tert-butyl dicarbonate (11.7 g) was added dropwise at room temperature, and the reaction solution was stirred at room temperature for 1 hour. The solvent was distilled away under reduced pressure, water (200 mL) was added to the residue, and extracted with ethyl acetate (200 mL). The extract was washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate, and then solvent was distilled away under reduced pressure. The residue was

purified by silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/ethanol 10:1) to give the title compound 17.2 g (yield 86%) as a white solid.

NMR ($CDCl_3$) δ 1.43-1.51 (12H, m), 2.98-3.17 (4H, m), 3.58-3.85 (4H, m), 4.47 (2H, q, J = 5.7 Hz), 6.36 (1H, d, J = 7.2 Hz), 7.22-7.28 (1H, m), 7.46 (1H, d, J = 10.8 Hz), 8.16 (1H, s).

13b) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine (8.26 g) obtained in Example 13a) in ethanol (80 mL) was added 8N aqueous solution of sodium hydroxide (5.5 mL), and stirred at room temperature for 30 minutes. To the reaction solution was added concentrated hydrochloric acid to neutralize under ice-cooling, and the solvent was distilled away under reduced pressure. To the residue was added water (50 mL) to dissolve, and adjusted to pH 3-4 by further adding concentrated hydrochloric acid under ice-cooling, then extracted with chloroform (100 mL). The extract was dried over anhydrous magnesium sulfate, and solvent was distilled away under reduced pressure, and then to the obtained residue was added a THF solution (68.2 mL) of 1.0M borane-THF complex, followed by stirring at room temperature for 1 hour under argon atmosphere. The

reaction solution was poured into ice-water (300 mL), and adjusted to pH 1-2 with concentrated hydrochloric acid, and then the mixture was stirred at room temperature for 1 hour. The mixture was adjusted to pH 10-11 with 8N aqueous solution of sodium hydroxide, and extracted with ethyl acetate (150 mL). The extract was washed with saturated saline (100 mL), dried over anhydrous magnesium sulfate, and then solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/ethanol 5:1) to give the title compound 4.77 g (yield 65%) as a white solid.

NMR ($CDCl_3$) δ 1.44 (9H, s), 2.94-3.10 (4H, m), 3.51-3.67 (4H, m), 4.61 (2H, d, J = 5.4 Hz), 5.16 (1H, t, J = 5.4 Hz), 6.41-6.45 (1H, m), 7.21-7.24 (2H, m), 7.60 (1H, s).

13c) 2-Hydroxymethyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine (3.99 g) obtained in Example 13b) was dissolved in concentrated hydrochloric acid (20 mL), and stirred at room temperature for 20 minutes. To the mixture was added a mixture of ethanol (50 mL) and 2-propanol (50 mL), the precipitated crystals were collected by filtration, followed by washing with 2-propanol (10 mL) and diethyl ether (20 mL), and then dried

under reduced pressure to give the title compound 3.66 g (yield 99.8%) as a white crystal.

NMR (D_2O) δ 3.41-3.56 (4H, m), 3.56-3.68 (4H, m), 4.90 (2H, s), 7.03 (1H, d, J = 7.6 Hz), 7.58 (1H, d, J = 9.2 Hz), 7.84 (1H, dd, J = 10.6, 7.6 Hz), 7.93 (1H, s).

13d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.14 g (yield 89%) was obtained as a colorless powder from 2-hydroxymethyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (0.92 g) obtained in Example 13c). This was crystallized from acetone-ethanol to give the title compound of white crystals 0.77 g (recovery rate 68%).

NMR ($CDCl_3$) δ 2.88-3.18 (6H, m), 3.56-3.92 (6H, m), 4.88 (2H, s), 6.27 (1H, d, J = 7.4 Hz), 7.19 (1H, dd, J = 9.2, 7.4 Hz), 7.37 (1H, d, J = 8.8 Hz), 7.52 (1H, s), 7.57-7.63 (1H, m), 7.94-7.98 (4H, m), 8.49 (1H, br), LC/MS 513 (M).

Elemental analysis for $C_{25}H_{25}ClN_4O_4S$

Calcd (%): C, 58.53; H, 4.91; N, 10.92

Found (%): C, 58.40; H, 4.84; N, 10.78.

Example 14

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-carbamoyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 8, the title

compound 0.22 g (yield 49%) was obtained as a colorless powder from 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-carboxy-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.50 g) obtained in Example 32.

NMR ($CDCl_3$) δ2.56-5.80 (12H, m), 6.26 (1H, d, J = 7.2 Hz), 6.80 (1H, br), 7.14 (1H, dd, 7.2 and 9.0 Hz), 7.44 (1H, d, J = 9.0 Hz), 7.61 (1H, dd, J = 9.0 and 1.8 Hz), 7.66 (1H, d, J = 1.5 Hz), 7.89-7.99 (4H, m), 8.38 (1H, s), 8.49 (1H, d, J = 1.5 Hz).

Elemental analysis for $C_{26}H_{25}ClN_5O_4S \cdot 0.5H_2O$

Calcd (%): C, 56.88 ; H, 4.96 ; N, 12.76

Found (%): C, 56.58 ; H, 5.16 ; N, 12.46.

Example 15

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-nitroimidazo[1,2-a]pyridine

15a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-3-nitroimidazo[1,2-a]pyridine

To a solution of 1-Boc-piperazine (14.0 g) and N-ethyldiisopropylamine (25.9 g) in 1-propanol (300 mL) was added 5-chloro-3-nitroimidazo[1,2-a]pyridine (9.88 g), and refluxed for 4 hours. The reaction solution was allowed to cool to room temperature, and concentrated under reduced pressure. The residue was crystallized from ethanol to give the title compound 17.4 g (yield 67%) as yellow crystals.

NMR ($CDCl_3$) δ 1.47 (9H, s), 2.50-3.40 (6H, m), 3.54-4.25 (2H, m), 6.67 (1H, d, J = 7.6 Hz), 7.50 (1H, d, J = 8.3 Hz), 7.59 (1H, dd, J = 8.3 and 7.6 Hz), 8.49 (1H, s).

15b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-nitroimidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-3-nitroimidazo[1,2-a]pyridine (17.4 g) obtained in Example 15a) in methanol (300 mL) was added 4N solution of hydrogen chloride in ethyl acetate (80 mL), and stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure, and the obtained residue was crystallized from ethanol to give 3-nitro-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride 16.0 g (quantitative) as yellow crystals. To a suspension of 3-nitro-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (9.61 g) in aceronitrile (300 mL) was added DBU (9.13 g), and stirred at room temperature for 10 minutes. 3-(6-Chloro-2-naphthyl)sulfonylpropionic acid (8.96 g) and HOBt (5.51 g) were added thereto, and cooled to 0°C. To this mixture were added triethylamine (6.07 g) and WSC (6.90 g), and stirred at room temperature for 2 days. The reaction solution was concentrated under reduced pressure, and the residue was diluted with 10% aqueous solution of sodium carbonate, followed by extracting with dichloromethane. The extract was washed

with saturated saline, dried over anhydrous magnesium sulfate, and concentrated. The obtained residue was purified by basic silica gel column chromatography (eluent: hexane/ethyl acetate 1:3), and crystallized from ethyl acetate to give the title compound 9.95 g (yield 63%) as a pale yellow crystal.

NMR ($CDCl_3$) δ 2.60-3.10 (5H, m), 3.10-3.95 (6H, m), 4.35-4.65 (1H, br), 6.66 (1H, dd, J = 7.4 and 1.6 Hz), 7.51-7.66 (3H, m), 7.89-7.99 (4H, m), 8.48 (1H, s), 8.51 (1H, s).

Elemental analysis for $C_{24}H_{22}ClN_5O_5S \cdot 0.1H_2O$

Calcd (%): C, 54.41; H, 4.22; N, 13.22

Found (%): C, 54.43; H, 4.47; N, 12.94

Example 16

3-Amino-5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine dihydrochloride

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-nitroimidazo[1,2-a]pyridine (8.24 g) obtained in Example 15, reduced iron (4.36 g) and calcium chloride (3.55 g) were added to a mixture of 80% ethanol (600 mL) and N,N-dimethylformamide (60 mL), and refluxed with heating overnight. The reaction solution was cooled to room temperature, and added reduced iron (4.36 g), followed by refluxing with heating further for 5 hours. The reaction solution was cooled to room temperature, filtered through a sellite, and the filtrate was

concentrated under reduced pressure. The obtained residue was diluted with 10% aqueous solution of sodium carbonate, and extracted with dichloromethane. The extract was washed with saturated saline, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by basic silica gel column chromatography (eluent: methanol/ethyl acetate 1:20), and dissolved in a mixture of ethyl acetate and ethanol, followed by adding 4N solution of hydrogen chloride in ethyl acetate (5 mL), and stirred under ice-cooling for 30 minutes. The precipitate was collected by filtration, washed with ethyl acetate, and dried to give the title compound 1.02 g (yield 11.4%) as a colorless crystal.

NMR (DMSO-d_6) δ 2.70-3.10 (4H, m), 3.20-3.36 (2H, m), 3.42-3.72 (3H, m), 3.82-3.94 (1H, m), 4.18-4.30 (1H, m), 5.00-6.20 (4H, br), 6.81 (1H, d, J = 7.0 Hz), 7.14 (1H, s), 7.48 (1H, d, J = 9.0 Hz), 7.61 (1H, dd, J = 9.0 and 7.0 Hz), 7.75 (1H, dd, J = 8.8 and 2.2 Hz), 8.01 (1H, dd, J = 8.8 and 2.0 Hz), 8.20 (1H, d, J = 8.8Hz), 8.28-8.34 (2H, m), 8.68 (1H, s), 13.95 (1H, bs).

Elemental analysis for $C_{24}H_{26}Cl_3N_5O_3S \cdot 0.3AcOEt$

Calcd (%): C, 50.67; H, 4.79; N, 11.72

Found (%): C, 50.95; H, 4.55; N, 11.75.

Example 17

5-[4-[3-[(1-tert-Butoxycarbonyl-5-chloro-2-

indolyl)sulfonyl]propionyl]-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine

According to a similar manner to Example 3e), the title compound 0.72 g (yield 78%) was obtained as a pale yellow powder from 2-hydroxymethyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (0.56 g) obtained in Example 13c).

NMR ($CDCl_3$) δ 1.75 (9H, s), 2.92-2.98 (6H, m), 2.59-2.88 (4H, m), 4.11 (2H, t, J = 8.2 Hz), 4.87 (2H, s), 6.28 (1H, d, J = 7.0 Hz), 7.20 (1H, dd, J = 8.8, 7.2 Hz), 7.37 (1H, d, J = 9.2 Hz), 7.46 (1H, dd, J = 9.2, 2.2 Hz), 7.51-7.53 (2H, m), 7.65-7.66 (1H, m), 8.0 (1H, d, J = 9.6 Hz).

Example 18

5-[4-[3-[(5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 4, the title compound 0.53 g (yield 82%) was obtained as a pale brown solid from 5-[4-[3-[(1-tert-butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine (0.72 g) obtained in Example 17.

NMR (DMSO-d_6) δ 2.85 (2H, t, J = 7.4 Hz), 2.93-3.08 (2H, m), 3.08-3.22 (2H, m), 3.22-3.56 (2H, m), 3.56-3.81 (4H, m), 4.76 (2H, s), 6.99 (1H, d, J = 7.4 Hz), 7.17-7.18 (1H, m),

7.34 (1H, dd, J = 8.8, 2.2 Hz), 7.53-7.63 (2H, m), 7.81-7.82 (1H, m), 7.91 (1H, t, J = 8.8 Hz), 8.08 (1H, s), LC/MS 502 (M-HCl).

Example 19

3-Acetylamino-5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine

To a solution of 3-amino-5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine dihydrochloride (0.29 g) obtained in Example 16 in pyridine (5 mL) was added acetic anhydride (0.09 g), and stirred at room temperature for 5 hours. The reaction solution was concentrated under reduced pressure, and the residue obtained was diluted with 10% aqueous solution of sodium carbonate, followed by extracting with dichloromethane. The extract was washed with saturated saline, dried over anhydrous magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (eluent: methanol containing 10% ammonia solution/dichloromethane 1:20), and crystallized from a mixture of ethyl acetate and diethyl ether to give the title compound 0.20 g (yield 76%) as a colorless crystal.

NMR ($CDCl_3$) δ 2.26 (3H, s), 2.38-2.88 (10H, m), 3.82-4.08 (1H, m), 4.54-4.76 (1H, m), 6.40-6.49 (1H, m), 7.08-7.22

(1H, m), 7.43-7.62 (2H, m), 7.91-8.03 (5H, m), 8.50 (1H, s), 10.19 (1H, s).

Elemental analysis for $C_{26}H_{26}ClN_5O_4S \cdot 0.6H_2O$

Calcd (%): C, 56.49; H, 4.98; N, 12.71

Found (%): C, 54.60; H, 4.89; N, 12.45

Example 20

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxy-2-propyl)imidazo[1,2-a]pyridine hydrochloride

20a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(2-hydroxy-2-propyl)imidazo[1,2-a]pyridine and 2-acetyl-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-3-methyl-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine (7.17 g) obtained in Example 48a) in THF (60 mL) was added dropwise 1M solution of methylmagnesium bromide in THF (60 mL) under argon atmosphere and ice-cooling. The mixture was stirred at room temperature for 30 minutes, and carefully poured into ice-water (100 mL), followed by extracting with ethyl acetate (100 mL). The organic layer was washed with saturated saline (100 mL), dried over anhydrous magnesium sulfate, and then solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/ethanol 10:1) to give 5-[4-(tert-

butoxycarbonyl)-1-piperazinyl]-2-(2-hydroxy-2-propyl)imidazo[1,2-a]pyridine 2.96 g (yield 41%) as a pale yellow powder and 2-acetyl-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine 2.82 g (yield 45%) as a pale yellow powder, respectively.

5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(2-hydroxy-2-propyl)imidazo[1,2-a]pyridine:

NMR ($CDCl_3$) δ 1.50 (9H, s), 1.69 (6H, s), 2.99-3.13 (4H, m), 3.58-3.77 (4H, m), 6.29 (1H, d, J = 7.0 Hz), 7.18 (1H, dd, J = 8.8, 7.0 Hz), 7.36 (1H, d, J = 8.8 Hz), 7.44 (1H, s).

2-Acetyl-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine:

NMR ($CDCl_3$) δ 1.51 (9H, s), 2.73 (3H, s), 2.98-3.17 (4H, m), 3.58-3.81 (4H, m), 6.37 (1H, d, J = 6.8 Hz), 7.27 (1H, d, J = 9.2, 7.2 Hz), 7.45 (1H, d, J = 9.2 Hz), 8.13 (1H, s).

20b) 2-(2-Hydroxy-2-propyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

According to a similar manner to Example 1b), the title compound 2.87 g (yield 86%) was obtained from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(2-hydroxy-2-propyl)imidazo[1,2-a]pyridine (3.61 g) obtained in Example 20a).

NMR (D_2O) δ 1.74 (6H, s), 3.48-3.58 (4H, m), 3.58-3.67 (4H, m), 7.09 (1H, d, J = 7.8 Hz), 7.59 (1H, d, J = 9.0 Hz), 7.79 (1H, s), 7.89 (1H, dd, J = 9.0, 7.8 Hz).

20c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxy-2-propyl)imidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.15 g (yield 85%) was obtained from 2-(2-hydroxy-2-propyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (1.00 g) obtained in Example 20b).

NMR ($CDCl_3$) δ 1.69 (6H, s), 2.90-3.19 (6H, m), 3.53-3.68 (2H, m), 3.68-3.94 (4H, m), 6.27 (1H, d, J = 7.4 Hz), 7.17 (1H, dd, J = 9.0, 7.2 Hz), 7.38 (1H, d, J = 9.2 Hz), 7.43 (1H, s), 7.58-7.63 (1H, m), 7.92-7.98 (4H, m), 8.49 (1H, s).

20d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxy-2-propyl)imidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 1d), the title compound 0.82 g (yield 89%) was obtained from 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxy-2-propyl)imidazo[1,2-a]pyridine (0.86 g) obtained in Example 20c).

NMR (DMSO-d_6) δ 1.63 (6H, s), 2.82 (2H, t, J = 7.2 Hz), 2.92-3.06 (2H, m), 3.06-3.20 (2H, m), 3.44-3.82 (6H, m), 6.97 (1H, d, J = 7.4 Hz), 7.59 (1H, d, J = 8.8 Hz), 7.74 (1H, dd, J = 8.8, 2.2 Hz), 7.83-8.04 (3H, m), 8.18-8.32 (3H, m), 8.67 (1H, br), LC/MS 542 (M-HCl).

Example 21

2-(Carbamoyloxymethyl)-5-[4-[3-[(6-chloro-2-

naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine

21a) 2-(Carbamoyloxymethyl)-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine (4.59 g) obtained in Example 13b) inTHF (50 mL) was added dropwise trichloroacetyl isocyanate (3.12 g) at room temperature. The mixture was stirred at room temperature for 20 minutes, and the solvent was distilled away under reduced pressure. The residue was dissolved in methanol (50 mL), and potassium carbonate (0.19 g) was added thereto, followed by stirring at room temperature for 1 hour. The solvent was distilled away under reduced pressure, water (50 mL) was added to the residue, and extracted with chloroform (100 mL). The extract was washed with saturated saline (100 mL), dried over anhydrous magnesium sulfate, and then solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 10:1) to give the title compound 3.52 g (yield 68%) as a colorless powder.

NMR ($CDCl_3$) δ 1.50 (9H, s), 2.97-3.14 (4H, m), 3.57-3.78 (4H, s), 4.84 (2H, br), 5.29 (2H, s), 6.30 (1H, d, J = 6.8 Hz), 7.19 (1H, dd, J = 8.8, 7.0 Hz), 7.37 (1H, d, J = 8.8 Hz), 7.59 (1H, s).

21b) 2-(Carbamoyloxymethyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

According to a similar manner to Example 1b), the title compound 2.26 g (yield 81%) was obtained as a white crystal from 2-(aminocarbonyloxymethyl)-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine (3.00 g) obtained in Example 21a).

NMR (D_2O) δ 3.47-3.58 (4H, m), 3.58-3.69 (4H, m), 5.36 (2H, s), 7.07 (1H, d, J = 7.6 Hz), 7.60 (1H, d, J = 8.8 Hz), 7.88 (1H, dd, J = 8.8, 7.6 Hz), 8.04 (1H, s).

21c) 2-(Carbamoyloxymethyl)-5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.04 g (yield 75%) was obtained as a white crystal from 2-(aminocarbonyloxymethyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (1.05 g) obtained in Example 21b).

NMR ($CDCl_3$) δ 2.88-3.18 (6H, m), 3.54-3.67 (2H, m), 3.67-3.93 (4H, m), 4.88 (2H, br), 5.29 (2H, s), 6.27 (1H, d, J = 7.4 Hz), 7.20 (1H, dd, J = 9.2, 7.4 Hz), 7.39 (1H, d, J = 9.2 Hz), 7.57-7.63 (2H, m), 7.94-7.98 (4H, m), 8.50 (1H, br), LC/MS 556 (M).

Example 22

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-

(methylcarbamoyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-carboxy-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0,40 g) obtained in Example 32, WSC (0.20 g) and HOBt (0.16 g) were dissolved in DMF (10 mL), and 40% aqueous solution of methylamine (0.1 g) was added thereto, followed bystirring for 10 minutes, and then triethylamine (0.42 g) was added and stirred at room temperature for 40 hours. The reaction solution was concentrated under reduced pressure, diluted with aqueous solution of sodium hydrogen carbonate, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue obtained was purified by basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 20:1), recrystallized from ethyl acetate-diethyl ether to give the title compound 0.22 g (yield 57%) as a pale yellow powder.

NMR ($CDCl_3$) δ2.52 (3H, s), 2.56-5.37 (14H, m), 6.20 (1H, dd, J = 7.5 and 1.2 Hz), 6.75 (1H, br), 7.08 (1H, dd, 7.2 and 9.0 Hz), 7.31 (1H, d, J = 8.7 Hz), 7.61 (1H, dd, J = 9.0 and 1.8 Hz), 7.90-7.99 (4H, m), 8.14 (1H, s), 8.49 (1H, s).

Elemental analysis for $C_{27}H_{28}ClN_5O_4S \cdot 0.5H_2O$

Calcd (%): C, 57.59; H, 5.19; N, 12.44

Found (%): C, 57.35; H, 5.22; N, 12.36.

Example 23

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-(methylthio)ethyl]carbamoyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 22, the title compound 0.32 g (yield 27%) was obtained as a colorless powder from 2-(methylthio)ethylamine (0.18 g).

NMR ($CDCl_3$) δ1.83-5.61 (21H, m), 6.22 (1H, d, J = 7.2 Hz), 7.03 (1H, br), 7.11 (1H, t, J = 8.1 Hz), 7.33 (1H, d, J = 9.0 Hz), 7.61-8.09 (6H, m), 8.50-8.56 (1H, m).

Elemental analysis for $C_{29}H_{32}ClN_5O_4S_2 \cdot H_2O \cdot 0.5EtOAc$

Calcd (%): C, 55.06; H, 5.66; N, 10.36

Found (%): C, 55.25; H, 5.67; N, 10.14.

Example 24

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(1-hydroxyethyl)imidazo[1,2-a]pyridine hydrochloride

24a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(1-hydroxyethyl)imidazo[1,2-a]pyridine

To a solution of 2-acetyl-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine (4.13 g) obtained in Example 20a) in ethanol (20 mL) was added sodium borohydride (0.55 g) at room temperature, and stirred at room temperature for 15 minutes, and then poured into ice-water (100 mL). The mixture was extracted with ethyl

acetate (100 mL), and the extract was washed with saturated saline (100 mL), dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 10:1) to give the title compound 3.95 g (yield 95%) as a colorless powder.

NMR (DMSO-d_6) δ 1.44-1.63 (12H, m), 2.94-3.12 (4H, m), 3.48-3.70 (4H, m), 4.77-4.95 (1H, m), 5.21 (1H, d, J = 4.8 Hz), 6.41-6.45 (1H, m), 7.17-7.30 (2H, m), 7.54 (1H, s).

24b) 2-(1-Hydroxyethyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

According to a similar manner to Example 1b), the title compound 2.87 g (yield 90%) was obtained from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(1-hydroxyethyl)imidazo[1,2-a]pyridine (3.46 g) obtained in Example 24a).

NMR (D_2O) δ 1.67 (3H, d, J = 6.6 Hz), 3.47-3.56 (4H, m), 3.56-3.68 (4H, m), 5.25 (1H, q, J = 6.6 Hz), 7.08 (1H, d, J = 7.6 Hz), 7.60 (1H, d, J = 9.2 Hz), 7.87-7.93 (2H, m).

24c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(1-hydroxyethyl)imidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.12 g (yield 85%) was obtained from 2-(1-hydroxyethyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (0.96 g) obtained in Example 24b).

NMR ($CDCl_3$) δ 1.66 (3H, d, J = 6.6 Hz), 2.88-3.19 (6H, m), 3.54-3.68 (2H, m), 3.68-3.95 (4H, m), 5.12 (1H, q, J = 6.6 Hz), 6.28 (1H, d, J = 7.4 Hz), 7.20 (1H, dd, J = 8.8, 7.4 Hz), 7.38 (1H, d, J = 8.8 Hz), 7.46 (1H, s), 7.61 (1H, dd, J = 9.2, 2.0 Hz), 7.90-7.95 (4H, m), 8.50 (1H, br).

24d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(1-hydroxyethyl)imidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 1d), the title compound 0.83 g (yield 73%) was obtained as a pale yellow powder from 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(1-hydroxyethyl)imidazo[1,2-a]pyridine (1.06 g) obtained in Example 24c).

NMR (DMSO-d_6) δ 1.56 (3H, d, J = 6.2 Hz), 2.73-2.90 (2H, t, J = 7.6 Hz), 2.90-3.08 (2H, m), 3.08-3.22 (2H, m), 3.22-3.56 (2H, m), 3.56-3.83 (4H, m), 5.07 (1H, q, J = 6.2 Hz), 6.11 (1H, br), 6.96 (1H, d, J = 7.8 Hz), 7.60 (1H, d, J = 8.8 Hz), 7.71-7.76 (1H, m), 7.86-8.04 (3H, m), 8.18-8.32 (3H, m), 8.68 (1H, br), LC/MS 529 (M+2-HCl).

Example 25

5-[3-[2-(Acetylamino)ethyl]carbamoyl-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

To a solution of 5-[4-[3-[(6-chloro-2-

naphthyl)sulfonyl]propionyl]-3-carboxyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (1.15 g) obtained in Example 32, WSC (0.58 g) and HOBt (0.46 g) in DMF (10 mL) were added tert-butoxycarbonylethylenediamine (0.32 g) and triethylamine (1.01 g), and stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure, diluted with aqueous solution of sodium hydrogen carbonate, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue obtained was purified by basic silica gel column chromatography (ethyl acetate → ethyl acetate/methanol 20:1) to give amide compound as a pale yellow powder 0.11 g. The amide compound obtained (0.11 g) was dissolved in concentrated hydrochloric acid (1 mL), and stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and the residue was dissolved in pyridine (2 mL), then acetic anhydride (0.3 mL) was added thereto, followed by stirring at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and purified by basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 20:1), recrystallized from ethyl acetate-diethyl ether to give the title compound 40 mg (yield 3%) as a colorless powder.

NMR ($CDCl_3$) δ2.38-5.31 (21H, m), 6.12-6.33 (2H, m), 7.07-7.13 (1H, m), 7.25-7.34 (1H, m), 7.42-7.63 (2H, m), 7.92-8.05 (4H, m), 8.49-8.53 (1H, m).

Elemental analysis for $C_{30}H_{33}ClN_6O_5S \cdot 1.6H_2O \cdot 0.4EtOAc$

Calcd (%): C, 55.07; H, 5.76; N, 12.19

Found (%): C, 54.93; H, 5.60; N, 12.05

Example 26

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-(carboxymethyl)carbamoyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine trifluoroacetate

To a solution of 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-carboxyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (1.15 g) obtained in Example 32, WSC (0.58 g) and HOBt (0.46 g) in DMF (10 mL) was added a solution of glycine tert-butyl ester hydrochloride (0.33 g), DBU (0.30 g) and triethylamine (1.01 g) in DMF (5 mL), and stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure, diluted with aqueous solution of sodium hydrogen carbonate, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue obtained was purified by basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 20:1) to give amide compound 0.21 g as a pale yellow powder. The amide

compound obtained (0.21 g) was dissolved in trifluoroacetic acid (1 mL), and stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure, and crystallized from ethyl acetate to give the title compound 50 mg (yield 4%) as a colorless powder.

NMR (CD_3OD) δ2.56 (3H, d, J = 0.9 Hz), 2.66-5.35 (13H, m), 6.90-8.63 (11H, m).

Elemental analysis for $C_{30}H_{29}ClF_3N_5O_8S \cdot 1.5H_2O \cdot 0.3EtOAc$

Calcd (%): C, 48.95; H, 4.53; N, 9.15

Found (%): C, 48.71; H, 4.36; N, 8.90.

Example 27

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-(methylsulfonyl)ethyl]carbamoyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-(methylthio)ethyl]carbamoyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.24 g) obtained in Example 23 and methanesulfonic acid (0.1 g) were dissolved in dichloromethane (7 mL), and a solution of 3-chloroperbenzoic acid (70%; 0.1 g) in dichloromethane (3 mL) was added dropwise at room temperature, followed by stirring at room temperature for 3 hours. To the reaction solution was added saturated aqueous solution of sodium thiosulfate, and stirred at room temperature for 1 hour. The reaction solution was diluted with aqueous solution of

sodium hydrogen carbonate, and organic layer was separated. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol 20:1 → 10:1) to give the title compound 60 mg (yield 24%) as a colorless powder.

NMR ($CDCl_3$) δ1.83-5.55 (21H, m), 6.22 (1H, d, J = 7.5 Hz), 7.11 (1H, dd, J = 9.0 and 7.2 Hz), 7.32-7.38 (2H, m), 7.61 (1H, dd, J = 2.1 and 8.7 Hz), 7.93-8.60 (6H, m).

Elemental analysis $C_{29}H_{32}ClN_5O_6S_2 \cdot 1.5H_2O \cdot 0.6Et_2O$

Calcd (%): C, 52.55; H, 5.76; N, 9.76

Found (%): C, 52.66; H, 5.36; N, 9.37.

Example 28

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-(methylsulfinyl)ethyl]carbamoyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-(methylthio)ethyl]carbamoyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.24 g) obtained in Example 23 and methanesulfonic acid (0.1 g) were dissolved in dichloromethane (7 mL), and a solution of 3-chloroperbenzoic acid (70%; 0.1 g) in dichloromethane (3 mL) was added dropwise at room temperature, followed by stirring at room temperature for 3 hours. To the reaction solution was added saturated aqueous solution of sodium

thiosulfate, and stirred at room temperature for 1 hour. The reaction solution was diluted with aqueous solution of sodium hydrogen carbonate, and organic layer was separated. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol 20:1 → 10:1) to give the title compound 70 mg (yield 29%) as a colorless powder.

NMR ($CDCl_3$) δ1.83-5.58 (21H, m), 6.21 (1H, d, J = 7.5 Hz), 7.12 (1H, dd, J = 9.0 and 7.2 Hz), 7.34 (1H, d, J = 8.7 Hz), 7.57-7.62 (2H, m), 7.82-8.59 (6H, m).

Elemental analysis for $C_{29}H_{32}ClN_5O_5S_2 \cdot 2H_2O \cdot 0.6Et_2O$

Calcd (%): C, 53.07 ; H, 5.96 ; N, 9.85

Found (%): C, 53.01 ; H, 5.54 ; N, 9.39.

Example 29

2-(N-Acetylaminomethyl)-5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine hydrochloride

29a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-phthalimidomethylimidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine (3.32 g) obtained in Example 13b) in THF (35 mL) were added triphenylphosphine (5.25 g) and phthalimide (2.94 g), diethyl azodicarboxylate (9.1 mL) was added dropwise

thereto under ice-cooling, and the mixture was stirred at room temperature for 16 hours. The solvent was distilled away under reduced pressure, ethyl acetate (10 mL) was added to the residue, and the precipitate was collected by filtration, washed with ethyl acetate (5 mL) and diethyl ether (10 mL), and dried under reduced pressure to give the title compound 3.32 g (yield 72%) as a white solid.
NMR ($CDCl_3$) δ 1.50 (9H, s), 2.97-3.12 (4H, m), 3.53-3.78 (4H, m), 5.07 (2H, s), 6.26 (1H, d, J = 7.4 Hz), 7.14 (1H, dd, J = 8.8, 7.0 Hz), 7.35 (1H, d, J = 8.8 Hz), 7.56 (1H, s), 7.67-7.77 (2H, m), 7.84-7.93 (2H, m).

29b) 2-Aminomethyl-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-phthalimidomethylimidazo[1,2-a]pyridine (6.70 g) obtained in Example 29a) in ethanol (70 mL) was added hydrazine monohydrate (2.1 mL), and refluxed for 1 hour. The generated precipitate was collected by filtration, and the solid was washed with ethanol (50 mL). The filtrate and washings were combined and concentrated under reduced pressure, to the residue was added 1N aqueous solution of sodium hydroxide (50 mL), and extracted with chloroform (100 mL). The extract was dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure to give the title compound 4.42 g (yield

92%) as a white solid.

NMR ($CDCl_3$) δ 1.51 (9H, s), 2.97-3.18 (4H, m), 3.57-3.79 (4H, m), 4.05 (2H, s), 6.28 (1H, d, J = 7.2 Hz), 7.18 (1H, dd, J = 9.2, 7.4 Hz), 7.33 (1H, d, J = 8.8 Hz), 7.46 (1H, s).

29c) 2-(N-Acetylaminomethyl)-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine

To a solution of 2-aminomethyl-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine (1.99 g) obtained in Example 29b) in acetonitrile (20 mL) was added triethylamine (3.3 mL), then acetic anhydride (1.1 mL), and stirred at room temperature for 1 hour. The deposited precipitate was collected by filtration, washed with acetonitrile (5 mL) and ether (5 mL), and dried under reduced pressure to give the title compound 1.97 g (yield 88%) as a white powder.

NMR ($CDCl_3$) δ 1.51 (9H, s), 2.02 (3H, s), 2.98-3.15 (4H, m), 3.59-3.77 (4H, m), 4.59 (2H, d, J = 5.6 Hz), 6.31 (1H, d, J = 7.0 Hz), 6.54 (1H, br), 7.20 (1H, dd, J = 8.8, 7.0 Hz), 7.32 (1H, d, J = 8.8 Hz), 7.50 (1H, s).

29d) 2-(N-Acetylaminomethyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

According to a similar manner to Example 1b), the title compound 1.12 g (yield 81%) was obtained from 2-(N-acetylaminomethyl)-5-[4-(tert-butoxycarbonyl)-1-

piperazinyl]imidazo[1,2-a]pyridine (1.49 g) obtained in Example 29c).

NMR (D_2O) δ 2.11 (3H, s), 3.48-3.59 (4H, m), 3.59-3.68 (4H, m), 4.67 (2H, s), 7.08 (1H, d, J = 7.6 Hz), 7.60 (1H, d, J = 8.8 Hz), 7.87 (1H, d, J = 7.6 Hz), 7.92 (1H, s).

29e) 2-(N-Acetylaminomethyl)-5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.25 g (yield 90%) was obtained from 2-(N-acetylaminomethyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (1.04 g) obtained in Example 29d).

NMR ($CDCl_3$) δ 2.02 (3H, s), 2.89-3.18 (6H, m), 3.53-3.67 (2H, m), 3.67-3.93 (4H, m), 4.59 (2H, d, J = 5.4 Hz), 6.28 (1H, d, J = 7.0 Hz), 6.48 (1H, br), 7.21 (1H, dd, J = 8.8, 7.0 Hz), 7.35 (1H, d, J = 8.8 Hz), 7.49 (1H, s), 7.61 (1H, dd, J = 8.8, 2.0 Hz), 7.90-8.00 (4H, m), 8.50 (1H, br).

29f) 2-(N-Acetylaminomethyl)-5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 1d), the title compound 0.98 g (yield 83%) was obtained as a white powder from 2-(N-acetylaminomethyl)-5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine (1.11 g) obtained in Example 29e).

NMR (DMSO-d_6) δ 1.94 (3H, s), 2.83 (2H, t, J = 7.4 Hz), 2.93-3.07 (2H, m), 3.07-3.18 (2H, m), 3.31-3.79 (6H, m), 4.53 (2H, d, J = 6.0 Hz), 6.97 (1H, d, J = 7.2 Hz), 7.63 (1H, d, J = 8.8 Hz), 7.74 (1H, dd, J = 8.8, 2.2 Hz), 7.91 (1H, dd, J = 8.8, 7.2 Hz), 8.01 (1H, dd, J = 8.8, 2.2 Hz), 8.09 (1H, s), 8.18-8.32 (3H, m), 8.67 (1H, br), 8.77 (1H, t, J = 6.0 Hz), LC/MS 554 (M-HCl).

Example 30

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(N-trifluoroacetylaminomethyl)imidazo[1,2-a]pyridine hydrochloride

30a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(N-trifluoroacetylaminomethyl)imidazo[1,2-a]pyridine

To a solution of 2-aminomethyl-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine (1.99 g) obtained in Example 29b) in acetonitrile (20 mL) was added triethylamine (3.3 mL), then ethyl trifluoroacetate (1.43 mL), and stirred at room temperature for 1 hour. The solvent was distilled away under reduced pressure, ether (5 mL) and acetonitrile (5 mL) were added to the residue, the resulting solid was collected by filtration, followed by washing with diethyl ether (5 mL), and dried under reduced pressure to give the title compound 2.33 g (yield 91%) as a white solid.

NMR ($CDCl_3$) δ 1.51 (9H, s), 3.00-3.17 (4H, m), 3.59-3.80

(4H, m), 4.68 (2H, d, J = 5.4 Hz), 6.34 (1H, d, J = 7.0 Hz), 7.20-7.35 (2H, m), 7.55 (1H, s), 8.15 (1H, br).

30b) 5-(1-piperazinyl)-2-(N-trifluoroacetylaminomethyl)imidazo[1,2-a]pyridine dihydrochloride

According to a similar manner to Example 1b), the title compound 1.36 g (yield 85%) was obtained from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(N-trifluoroacetylaminomethyl)imidazo[1,2-a]pyridine (1.71 g) obtained in Example 30a).

NMR (D_2O) δ 3.44-3.57 (4H, m), 3.57-3.64 (4H, m), 4.79 (2H, s), 6.99 (1H, d, J = 7.6 Hz), 7.55 (1H, d, J = 7.0 Hz), 7.79 (1H, dd, J = 7.6, 7.0 Hz), 7.95 (1H, br).

30c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(N-trifluoroacetylaminomethyl)imidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.37 g (yield 92%) was obtained as a white powder from 5-(1-piperazinyl)-2-(N-trifluoroacetylaminomethyl)imidazo[1,2-a]pyridine dihydrochloride (1.20 g) obtained in Example 30b).

NMR ($CDCl_3$) δ 2.90-3.21 (6H, m), 3.57-3.69 (2H, m), 3.69-3.94 (4H, m), 4.77 (2H, d, J = 5.6 Hz), 6.32 (1H, d, J = 7.0 Hz), 7.20-7.36 (2H, m), 7.56-7.63 (2H, m), 7.88-7.98 (4H, m), 8.50 (2H, br).

30d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(N-trifluoroacetylaminomethyl)imidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 1d), the title compound 1.11 g (yield 86%) was obtained as a white powder from 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(N-trifluoroacetylaminomethyl)imidazo[1,2-a]pyridine (1.19 g) obtained in Example 30c).

NMR (DMSO-d_6) δ 2.83 (2H, t, J = 7.0 Hz), 2.93-3.08 (2H, m), 3.08-3.20 (2H, m), 3.54-3.78 (6H, m), 4.72 (2H, d, J = 5.2 Hz), 6.96 (1H, d, J = 7.4 Hz), 7.64 (1H, d, J = 8.8 Hz), 7.74 (1H, d, J = 8.8, 2.0 Hz), 7.90 (1H, dd, J = 8.8, 7.4 Hz), 8.02 (1H, dd, J = 8.8, 2.0 Hz), 8.16-8.28 (4H, m), 8.69 (1H, br), LC/MS 608 (M-HCl).

Example 31

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

31a) 5-Fluoro-2-methylimidazo[1,2-a]pyridine

A solution of 2-amino-6-fluoropyridine (Ikemoto et al., Tetrahedron, 2002, Vol. 58, p. 489) (5.61 g) and bromoacetone (90%; 7.0 mL) in ethanol (50 mL) was refluxed for 18 hours. The mixture was concentrated under reduced pressure, and the residue was diluted with water. After

washing with ethyl acetate, it was made alkaline with aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the title compound 2.1 g (yield 28%) as a brown oil.

NMR ($CDCl_3$) δ2.49 (3H, s), 6.39-6.43 (1H, m), 7.12-7.20 (1H, m), 7.35 (1H, d, J = 8.4 Hz), 7.41 (1H, s).

31b) 5-[3-(tert-Butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 7a), the title compound 2.70 g (yield 64%) was obtained as a brown oil from 5-fluoro-2-methylimidazopyridine (2.0 g) obtained in Example 31a).

NMR ($CDCl_3$) δ1.51 (9H, s), 2.48 (3H, d, J = 0.6 Hz), 2.85-3.69 (8H, m), 6.28 (1H, dd, J = 1.5 and 10.5 Hz), 7.10-7.18 (1H, m), 7.28-7.41 (2H, m).

31c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 7b), the title compound 9.50 g (yield 36%) was obtained as a colorless powder from 5-[3-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine (13.9 g) obtained in Example 31b).

NMR ($CDCl_3$) δ1.47 (9H, s), 2.47-2.48 (3H, m), 2.72-5.16

(11H, m), 6.24 (1H, dd, J = 0.9 and 7.2 Hz), 7.13 (1H, dt, J = 7.2 and 1.5 Hz), 7.32-7.50 (2H, m), 7.60 (1H, dd, J = 9.0 and 1.5 Hz), 7.90-8.01 (4H, m), 8.49 (1H, s).

Elemental analysis for $C_{30}H_{33}ClN_4O_5S \cdot 0.5H_2O \cdot 0.2EtOAc$

Calcd (%): C, 59.31 ; H, 5.75 ; N, 8.98

Found (%): C, 59.21 ; H, 5.92 ; N, 8.79.

Example 32

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-carboxy-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 10, the title compound 2.80 g (yield 97%) was obtained as a brown powder from 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (3.0 g) obtained in Example 31.

NMR (DMSO-d_6) δ2.50-5.10 (11H, m), 7.00 (1H, dd, J = 3.3 and 7.2 Hz), 7.63 (1H, d, J = 8.7 Hz), 7.75 (1H, dt, J = 1.8 and 9.0 Hz), 7.87-8.06 (3H, m), 8.19 (1H, dd, J = 4.2 and 9.0 Hz), 8.26-8.31 (2H, m), 8.68 (1H, dd, J = 1.5 and 8.1 Hz).

Elemental analysis for $C_{26}H_{26}Cl_2N_4O_5S \cdot 0.2acetone \cdot H_2O$

Calcd (%): C, 52.62 ; H, 4.85 ; N, 9.23

Found (%): C, 52.90 ; H, 4.90 ; N, 9.04.

Example 33

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-(2-

pyridyl)methylcarbamoyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

To a solution of 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-carboxy-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (1.15 g) obtained in Example 32, DBU (0.30 g), WSC (0.58 g) and HOBt (0.46 g) in DMF (20 mL) was added 2-picolylamine (0.43 g), and stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure, diluted with aqueous solution of sodium hydrogen carbonate, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue obtained was purified by basic silica gel column chromatography (ethyl acetate → ethyl acetate/methanol 20:1) to give the title compound 0.49 g (yield 39%) as a pale yellow powder.

NMR($CDCl_3$) δ2.44 (3H, s), 2.62-3.04 (3H, m), 3.21-3.88 (6H, m), 4.06-4.38 (2H, m), 4.57-4.76 (2H, m), 5.40 (1H, s), 6.22 (1H, d, J = 7.2 Hz), 7.09-7.34 (5H, m), 7.60-7.98 (7H, m), 8.41-8.48 (2H, m).

Elemental analysis for $C_{32}H_{31}ClN_6O_4S \cdot H_2O \cdot 0.3EtOAc$

Calcd (%): C, 59.02; H, 5.28; N, 12.44

Found (%): C, 58.95; H, 5.09; N, 12.17.

Example 34

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-

ethoxycarbonylmethyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

34a) 5-(3-Ethoxycarbonylmethyl-1-piperazinyl)-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 7a), the title compound 3.70 g (yield 60%) was obtained as a brown oil from ethyl piperazin-2-acetate (14.0 g).

NMR ($CDCl_3$) δ1.21-1.31 (3H, m), 1.72-3.44 (13H, m), 4.10-4.21 (2H, m), 6.23 (1H, d, J = 7.2 Hz), 7.12 (1H, dd, J = 7.2 and 9.0 Hz), 7.28-7.31 (2H, m).

34b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-ethoxycarbonylmethyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 7b), the title compound 0.18 g (yield 62%) was obtained as a pale yellow powder from 5-(3-ethoxycarbonylmethyl-1-piperazinyl)-2-methylimidazo[1,2-a]pyridine (0.15 g) obtained in Example 34a).

NMR ($CDCl_3$) δ1.18-1.30 (3H, m), 2.48 (3H, s), 2.56-5.17 (15H, m), 6.23 (1H, dd, J = 1.3 and 6.9 Hz), 7.14 (1H, dd, J = 7.2 and 8.8 Hz), 7.27-7.36 (2H, m), 7.57-7.63 (1H, m), 7.95-7.99 (4H, m), 8.51 (1H, d, J = 4.4 Hz).

Elemental analysis for $C_{29}H_{31}ClN_4O_5S \cdot 0.7H_2O$

Calcd (%): C, 58.47; H, 5.48; N, 9.40

Found (%): C, 58.44; H, 5.56; N, 9.13.

Example 35

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-hydroxymethyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

35a) 5-(3-Hydroxymethyl-1-piperazinyl)-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 7a), the title compound 4.0 g (yield 83%) was obtained as a brown oil from piperazin-2-methanol (6.82 g).

NMR ($CDCl_3$) δ2.47 (3H, s), 2.65-3.76 (11H, m), 6.25 (1H, dd, J = 0.9 and 7.2 Hz), 7.12 (1H, dd, J = 7.2 and 9.0 Hz), 7.23-7.35 (2H, m).

35b) 5-[3-[(tert-Butyldimethylsilyloxy)methyl]-1-piperazinyl)-2-methylimidazo[1,2-a]pyridine

To a solution of 5-(3-hydroxymethyl-1-piperazinyl)-2-methylimidazo[1,2-a]pyridine (2.0 g) obtained in Example 35a) and imidazole (2.65 g) in DMF (20 mL) was added tert-butyldimethylchlorosilane (2.94 g), and stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, and diluted with aqueous solution of sodium carbonate and ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform → chloroform/methanol 20:1) to give the title compound 1.25 g (yield 43%) as a

brown oil.

NMR ($CDCl_3$) δ0.00-0.13 (6H, m), 0.85-0.93 (9H, m), 2.09 (3H, s), 2.47-3.76 (10H, m), 6.24 (1H, d, J = 7.2 Hz), 7.14 (1H, dd, J = 7.2 and 9.0 Hz), 7.25-7.32 (2H, m).

35c) 5-[3-[(tert-Butyldimethylsilyloxy)methyl]-4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

To a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoic acid (1.04 g), WSC (1.0 g) and HOBt (0.80 g) in DMF (20 mL) was added a solution of 5-[3-[(tert-butyldimethylsilyloxy)methyl]-1-piperazinyl)-2-methylimidazo[1,2-a]pyridine (1.25 g) obtained in Example 35b) in DMF (5 mL), and stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure, diluted with aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue obtained was purified by basic silica gel column chromatography (eluent: ethyl acetate) and silica gel column chromatography (eluent: chloroform → chloroform/methanol 20:1) to give the title compound 540 mg (yield 24%) as a brown oil.

35d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-hydroxymethyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

hydrochloride

To a solution of 5-[3-[(tert-butyldimethylsilyloxy)methyl]-4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.27 g) obtained in Example 35c) in acetonitrile (10 mL) was added dropwise 48% hydrofluoric acid at 0°C, and stirred at 0°C for 1 hour and at room temperature for 2 hours. To the reaction solution was added an aqueous solution of potassium carbonate to make it alkaline, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The compound obtained by purifying the residue with basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 20:1) was dissolved in ethanol (2 mL), and added 4N ethyl acetate solution of hydrogen chloride (0.5 mL) thereto, followed by concentrating under reduced pressure. The residue was recrystallized from ethyl acetate to give the title compound 120 mg (yield 51%) as a white powder.

NMR (CD_3OD) δ2.56 (3H, s), 2.68-4.59 (14H, m), 6.94-7.16 (1H, m), 7.50-7.67 (2H, m), 7.85-8.14 (6H, m), 8.56-8.58 (1H, m).

Elemental analysis for $C_{26}H_{28}Cl_2N_4O_4S \cdot 1.5H_2O \cdot 0.3EtOAc$

Calcd (%): C, 52.95; H, 5.46; N, 9.08

Found (%): C, 52.75 ; H, 5.62 ; N, 8.83.

Example 36

2-(N-Acetylaminomethyl)-5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-chloroimidazo[1,2-a]pyridine

36a) 2-(N-Acetylaminomethyl)-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-3-chloroimidazo[1,2-a]pyridine

N-Chlorosuccinimide (0.76 g) was added to a solution of 2-(N-acetylaminomethyl)-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine (1.6 g) in chloroform (12 mL), and stirred at at room temperature for 1 hour. The reaction solution was washed sequentially with saturated aqueous solution of sodium hydrogen carbonate (20 mL) and saturated saline (20 mL), and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/ethanol 5:1 → 1:1) to give the title compound 980 mg (yield 56%) as a white solid.

NMR ($CDCl_3$) δ 1.49 (9H, s), 2.06 (3H, s), 2.75 (2H, t, J = 9.6 Hz), 3.28 (4H, d, J = 9.6 Hz), 4.11 (2H, bs), 4.56 (2H, d, J = 5.1 Hz), 6.36 (1H, bs), 6.37 (1H, dd, J = 7.2, 0.9 Hz), 7.15 (1H, dd, J = 9.0, 7.2Hz), 7.30 (1H, dd, J = 9.0, 0.9 Hz), LC/MS 408 (MH^+).

36b) 2-(N-Acetylaminomethyl)-5-[4-[3-[(6-chloro-2-

naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-chloroimidazo[1,2-a]pyridine

2-(N-Acetylaminomethyl)-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-3-chloroimidazo[1,2-a]pyridine (0.72 g) was added to concentrated hydrochloric acid (10 mL) and dissolved. To this solution was added ethanol (50 mL), and concentrated under reduced pressure. To the residue was added again ethanol, and concentrated again under reduced pressure. To the residue was added isopropyl alcohol, and the precipitate was collected by filtration. The solid obtained was washed sequentially with isopropyl alcohol, and diethyl ether, and dried under reduced pressure to give 2-(N-acetylaminomethyl)-5-(1-piperazinyl)-3-chloroimidazo[1,2-a]pyridine dihydrochloride as a white solid.

To a suspension of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoic acid (0.37 g) in acetonitrile (10 mL) were added sequentially HOBt·H_2O (0.29 g) and WSC (0.36 g), and stirred at at room temperature for 20 minutes. To this reaction solution was added a solution of 2-(N-acetylaminomethyl)-5-(1-piperazinyl)-3-chloroimidazo[1,2-a]pyridine dihydrochloride previously obtained (0.57 g), DBU (450 mL) and triethylamine (553 mL) in acetonitrile (10 mL), and stirred at at room temperature for 2 hours. The solvent was distilled away under reduced pressure, and to

the residue were added chloroform (100 mL) and water (100 mL). The organic layer was separated, washed with saturated saline (100 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol 5:1), and recrystallized from chloroform/acetonitrile to give the title compound 540 mg (yield 73%) as a white crystal.

NMR ($CDCl_3$) δ 2.06 (3H, s), 2.67-2.78 (2H, m), 2.90-3.05 (3H, m), 3.28-3.38 (2H, m), 3.55-3.64 (3H, m), 3.86 (1H, d, J = 15.0 Hz), 4.52 (1H, bs), 4.56 (2H, d, J = 4.5 Hz), 6.32-6.35 (2H, m), 7.16 (1H, dd, J = 9.0, 7.2 Hz), 7.32 (1H, dd, J = 9.0, 0.9 Hz), 7.59 (1H, dd, J = 9.0, 2.1 Hz), 7.90-7.97 (4H, m), 8.48 (1H, s), LC/MS 588 (MH^+),

Elemental analysis for $C_{27}H_{27}Cl_2N_5O_4S$

Calcd (%): C, 55.10 ; H, 4.62 ; N, 11.90

Found (%): C, 54.74 ; H, 4.71 ; N, 11.86.

Example 37

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-(carbamoyl)methyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

37a) 5-[4-(tert-Butoxycarbonyl)-3-ethoxycarbonylmethyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

To a solution of 5-(3-ethoxycarbonylmethyl-1-piperazinyl)-2-methylimidazo[1,2-a]pyridine (3.50 g)

obtained in Example 34a) in ethanol (50 mL) was added dropwise di-tert-butyl dicarbonate (3.03 g), and stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure, diluted with aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract was washed with saturated saline, dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue obtained was purified by silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 10:1) to give the title compound 2.65 g (yield 57%) as a brown oil.

NMR ($CDCl_3$) δ1.22-1.28 (3H, m), 1.50 (9H, s), 2.47 (3H, s), 2.65-4.77 (11H, m), 6.24 (1H, dd, J = 1.5 and 7.2 Hz), 7.10-7.32 (3H, m).

37b) 5-[4-(tert-Butoxycarbonyl)-3-carboxymethyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

5-[4-(tert-Butoxycarbonyl)-3-ethoxycarbonylmethyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (2.60g) obtained in Example 37a) was dissolved in 1N sodium hydroxide (13 mL) and ethanol (10 mL), and stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure, and adjusted pH 4 with 0.5N hydrochloric acid, and then washed with ethyl acetate. Sodium chloride was added to the aqueous layer, and the

precipitate was collected by filtration, followed by washing with small amount of water to give the title compound 1.80 g (yield 74%) as a pale brown powder.

NMR (CD_3OD) δ1.50 (9H, s), 2.57 (3H, d, J = 0.8 Hz), 2.70-3.60 (7H, m), 4.07-4.15 (1H, m), 4.78 (1H, br), 7.03 (1H, dd, , J = 0.7 and 7.7 Hz), 7.53 (1H, d, J = 8.8 Hz), 7.86 (1H, dd, , J = 1.0 and 8.8 Hz), 7.92 (1H, d, J = 2.0 Hz).

37c) 5-[3-(Carbamoyl)methyl-4-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

A solotion of 5-[4-(tert-butoxycarbonyl)-3-carboxymethyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.56 g) obtained in Example 37b), HOBt-NH_3 complex (0.38 g) and WSC (0.43 g) in DMF (5 mL) was stirred at room temperature for 4 days. The reaction mixture was concentrated under reduced pressure, and diluted with aqueous sodium hydrogen carbonate solution and ethyl acetate. The precipitate was collected by filtration, and washed with ethyl acetate to give the title compound 0.37 g (yield 66%) as a white powder.

NMR ($CDCl_3$) δ1.51 (9H, s), 2.48 (3H, d, J = 0.8 Hz), 2.64-3.05 (8H, m), 4.11-4.16 (1H, m), 4.76 (1H, br), 5.40 (1H, br), 6.25 (1H, dd, J = 0.9 and 7.1 Hz), 7.14 (1H, dd, J = 7.2 and 8.8 Hz), 7.27-7.37 (2H, m).

37d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-(carbamoyl)methyl-1-piperazinyl]-2-methylimidazo[1,2-

a]pyridine

5-[3-(Carbamoyl)methyl-4-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.27 g) obtained in Example 37c) was dissolved in concentrated hydrochloric acid (1.5 mL), and stirred at room temperature for 10 minutes. The reaction solution was concentrated under reduced pressure, and to the residue obtained by azeotropic distillation with ethanol was added DBU (0.18 g) and dissolved in DMF (3 mL). This solution was added to a solution of 3-[(6-Chloro-2-naphthyl)sulfonyl]propanoic acid (0.17 g), HOBt (0.13 g) and WSC (0.17 g) in DMF (5 mL), and stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, and diluted with aqueous sodium carbonate solution, then extracted with THF and ethyl acetate. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 10:1) to give the title compound 0.13 g (yield 39%) as a white powder.

NMR ($CDCl_3$) δ2.49 (3H, s), 2.67-6.10 (15H, m), 6.22-6.25 (1H, m), 7.07-7.38 (3H, m), 7.58-7.63 (1H, m), 7.85-8.00 (4H, m), 8.51 (1H, d, J = 4.8 Hz).

Elemental analysis for $C_{27}H_{28}ClN_5O_4S \cdot H_2O$

Calcd (%): C, 56.69; H, 5.29; N, 12.24

Found (%): C, 56.43; H, 5.68; N, 12.51.

Example 38

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-(methylcarbamoyl)methyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

38a) 5-[3-(Methylcarbamoyl)methyl-4-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

5-(3-carboxymethyl-1-piperazinyl)-2-methylimidazo[1,2-a]pyridine (0.56 g) obtained in Example 37b), HOBt (0.35 g) and WSC (0.43 g) were dissolved in DMF (5 mL), and aqueous methylamine solution (40%; 0.16 mL) was added thereto, followed by stirring at room temperature for 4 days. The reaction mixture was concentrated under reduced pressure, and diluted with aqueous sodium carbonate solution and ethyl acetate. The organic layer was separated, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethyl acetate to give the title compound 0.37 g (yield 64%) as a colorless powder.

NMR ($CDCl_3$) δ1.51 (9H, s), 2.48 (3H, d, J = 0.8 Hz), 2.64-3.43 (11H, m), 4.07-4.14 (1H, m), 4.76 (1H, br), 6.24 (1H, dd, J = 0.8 and 7.2 Hz), 7.14 (1H, dd, J = 7.2 and 8.8 Hz), 7.27-7.37 (2H, m).

38b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-(methylcarbamoyl)methyl-1-piperazinyl]-2-methylimidazo[1,2-

a]pyridine

According to a similar manner to Example 37d), the title compound 0.12 g (yield 38%) was obtained as a colorless powder from 5-[3-(methylcarbamoyl)methyl-4-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.26 g) obtained in Example 38a).

NMR ($CDCl_3$) δ2.47 (3H, d, J = 2.2 Hz), 2.53-6.18 (17H, m), 6.18-6.22 (1H, m), 7.09-7.38 (3H, m), 7.56-7.62 (1H, m), 7.93-7.99 (4H, m), 8.50 (1H, d, J = 7.8 Hz).

Elemental analysis for $C_{28}H_{30}ClN_5O_4S \cdot H_2O$

Calcd (%): C, 57.38 ; H, 5.50 ; N, 11.95

Found (%): C, 57.54 ; H, 5.46 ; N, 11.67.

Example 39

(+)-5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(1-hydroxyethyl)imidazo[1,2-a]pyridine

The racemic 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine (0.18 g) obtained in Example 24c was optically resolved with HPLC using chiral stationary phase (CHIRALPAK AS 4.6 mm x 25 mm, eluent; hexane/ethanol 70:30), and as the anterior ingredient of two main fractions, the title compound 80 mg (optical purity more than 99.9%) was obtained as a pale yellow powder.

NMR ($CDCl_3$) δ 1.66 (3H, d, J = 6.6 Hz), 2.88-3.19 (6H, m),

3.54-3.68 (2H, m), 3.68-3.95 (4H, m), 5.12 (1H, q, J = 6.6 Hz), 6.28 (1H, d, J = 7.4 Hz), 7.20 (1H, dd, J = 8.8, 7.4 Hz), 7.38 (1H, d, J = 8.8 Hz), 7.46 (1H, s), 7.61 (1H, dd, J = 9.2, 2.0 Hz), 7.90-7.95 (4H, m), 8.50 (1H, br).

Example 40

(-)-5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(1-hydroxyethyl)imidazo[1,2-a]pyridine

The racemic 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine (0.18 g) obtained in Example 24c was optically resolved with HPLC using chiral stationary phase (CHIRALPAK AS 4.6 mm x 25 mm, eluent; hexane/ethanol 70:30), and as the posterior ingredient of two main fractions, the title compound 83 mg (optical purity more than 99.9%) was obtained as a pale yellow powder.

NMR ($CDCl_3$) δ 1.66 (3H, d, J = 6.6 Hz), 2.88-3.19 (6H, m), 3.54-3.68 (2H, m), 3.68-3.95 (4H, m), 5.12 (1H, q, J = 6.6 Hz), 6.28 (1H, d, J = 7.4 Hz), 7.20 (1H, dd, J = 8.8, 7.4 Hz), 7.38 (1H, d, J = 8.8 Hz), 7.46 (1H, s), 7.61 (1H, dd, J = 9.2, 2.0 Hz), 7.90-7.95 (4H, m), 8.50 (1H, br).

Example 41

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-(2-hydroxyethyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

41a) 5-[4-(tert-Butoxycarbonyl)-3-(2-hydroxyethyl)-1-

piperazinyl]-2-methylimidazo[1,2-a]pyridine

5-[4-(tert-Butoxycarbonyl)-3-carboxymethyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.75 g) obtained in Example 37b) was added by portions at room temperature to a solution of !M borane-THF complex in THF (5 mL), and stirred at room temperature for 2 hours. The reaction solution was poured into ice-water, and stirred for 10 minutes. After adjusting to pH 2 with concentrated hydrochloric acid, it was stirred at 0°C for 1.5 hours. To the reaction solution was added an aqueous solution of sodium hydrogen carbonate to make it alkaline, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the title compound 0.48 g (yield 67%) as a pale yellow powder.

NMR ($CDCl_3$) δ1.52 (9H, s), 1.80-4.57 (14H, m), 6.23 (1H, dd, J = 0.9 and 6.6 Hz), 7.13 (1H, dd, J = 6.9 and 9.0 Hz), 7.25-7.32 (2H, m).

41b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-(2-hydroxyethyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 37, the title compound 0.15 g (yield 31%) was obtained as a colorless powder from 5-[4-(tert-butoxycarbonyl)-3-(2-hydroxyethyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.48 g)

obtained in Example 41a).

NMR ($CDCl_3$) δ2.48 (3H, s), 2.70-4.85 (16H, m), 6.20-6.24 (1H, m), 7.11-7.35 (3H, m), 7.57-7.62 (1H, m), 7.91-7.97 (4H, m), 8.49 (1H, m).

Elemental analysis for $C_{27}H_{29}ClN_4O_4S \cdot H_2O$

Calcd (%): C, 58.00 ; H, 5.59 ; N, 10.02

Found (%): C, 57.74 ; H, 5.86 ; N, 10.31.

Example 42

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(N-methanesulfonylaminomethyl)imidazo[1,2-a]pyridine

42a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(N-methanesulfonylaminomethyl)imidazo[1,2-a]pyridine

To a solution of 2-aminomethyl-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine (1.99 g) obtained in Example 29b) in THF (20 mL) was added under ice-cooling sequentially triethylamine (3.3 mL), then methanesulfonyl chloride (0.56 mL), and the mixture was stirred at room temperature for 30 minutes. The formed precipitate was collected by filtration, washed with ethyl acetate (5 mL), then the filtrate and washings were combined and concentrated under reduced pressure. To the residue was added water (50 mL), and extracted with ethyl acetate (50 mL). The extract was dried over anhydrous magnesium sulfate, and solvent was distilled away under

reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 10:1) to give the title compound 2.11 g (yield 91%) as a white solid.

NMR ($CDCl_3$) δ 1.51 (9H, s), 2.86 (3H, s), 2.97-3.13 (4H, m), 4.59-4.78 (4H, m), 4.52 (2H, d, J = 6.2 Hz), 6.18 (1H, t, J = 6.2 Hz), 6.33 (1H, d, J = 7.4 Hz), 7.23 (1H, dd, J = 8.8, 7.4 Hz), 7.39 (1H. d, J = 8.8 Hz), 7.54 (1H, s).

42b) 2-(N-Methanesulfonylaminomethyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

According to a similar manner to Example 1b), the title compound 1.32 g (yield 86%) was obtained from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(N-methanesulfonylaminomethyl)imidazo[1,2-a]pyridine (1.64 g) obtained in Example 42a).

NMR (D_2O) δ 3.17 (3H, s), 3.43-3.57 (4H, m), 3.57-3.68 (4H, m), 4.63 (2H, s), 7.03 (1H, d, J = 7.8 Hz), 7.58 (1H, d, J = 8.8 Hz), 7.84 (1H, dd, J = 8.8, 7.8 Hz), 7.95 (1H, s).

42c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(N-methanesulfonylaminomethyl)imidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.25 g (yield 85%) was obtained as a white solid from 2-(N-methanesulfonylaminomethyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (1.15 g)

obtained in Example 42b).

NMR ($CDCl_3$) δ 2.88 (3H, s), 2.90-3.17 (6H, m), 3.53-3.68 (2H, m), 3.68-3.90 (4H, m), 4.52 (2H, d, J = 5.8 Hz), 6.27 (1H, br), 6.30 (1H, d, J = 7.4 Hz), 2.22 (1H, dd, J = 8.8, 7.4 Hz), 7.40 (1H, d, J = 8.8 Hz), 7.54 (1H, s), 7.60 (1H, dd, J = 9.2, 2.2 Hz), 7.94-7.98 (4H, m), 8.50 (1H, s), LC/MS 590 (M).

Example 43

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(N-trifluoromethanesulfonylaminomethyl)imidazo[1,2-a]pyridine hydrochloride

43a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(N-trifluoromethanesulfonylaminomethyl)imidazo[1,2-a]pyridine

To a solution of 2-aminomethyl-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine (1.99 g) obtained in Example 29b) in acetonitrile (20 mL) was added at room temperature sequentially triethylamine (3.3 mL), then N-phenyltrifluoromethanesulfonimide (4.29 g), and stirred at room temperature for 1 hour. The solvent was distilled away under reduced pressure, and to the residue was added water (50 mL), and extracted with ethyl acetate (50 mL). The extract was dried over anhydrous magnesium sulfate, and solvent was distilled away under reduced pressure. The residue was purified by silica gel column

chromatography (eluent: ethyl acetate/ethanol 10:1) to give the title compound 2.45 g (yield 88%) as a white solid.
NMR ($CDCl_3$) δ 1.51 (9H, s), 2.97-3.16 (4H, m), 3.60-3.81 (4H, m), 4.64 (2H, s), 6.34 (1H, d, J = 7.0 Hz), 7.24 (1H, dd, J = 8.8, 7.0 Hz), 7.43 (1H, d, J = 8.8 Hz), 7.55 (1H, s).

43b) 5-(1-Piperazinyl)-2-(N-trifluoromethanesulfonylaminomethyl)imidazo[1,2-a]pyridine dihydrochloride

According to a similar manner to Example 1b), the title compound 1.36 g (yield 78%) was obtained as a white crystal from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(N-trifluoromethanesulfonylaminomethyl)imidazo[1,2-a]pyridine (1.85 g) obtained in Example 43a).
NMR (D_2O) δ 3.43-3.57 (4H, m), 3.57-3.68 (4H, m), 4.76 (2H, s), 7.07 (1H, d, J = 7.8 Hz), 7.61 (1H, d, J = 8.8 Hz), 7.89 (1H, dd, J = 8.8, 7.8 Hz), 7.97 (1H, s).

43c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(N-trifluoromethanesulfonylaminomethyl)imidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.42 g (yield 88%) was obtained as a colorless powder from 5-(1-piperazinyl)-2-(N-trifluoromethanesulfonylaminomethyl)imidazo[1,2-a]pyridine dihydrochloride (1.31 g) obtained in Example 43b).

NMR ($CDCl_3$) δ 2.88-3.21 (6H, m), 3.54-3.68 (2H, m), 3.68-4.92 (4H, m), 4.65 (2H, s), 6.33 (1H, d, J = 7.0 Hz), 7.25 (1H, dd, J = 8.8, 7.0 Hz), 7.47 (1H, d, J = 8.8 Hz), 7.55 (1H, s), 7.61 (1H, dd, J = 8.8, 2.2 Hz), 7.94-7.99 (4H, m), 8.50 (1H, br).

43d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(N-trifluoromethanesulfonylaminomethyl)imidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 1d), the title compound 1.12 g (yield 82%) was obtained as a white powder from 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(N-trifluoromethanesulfonylaminomethyl)imidazo[1,2-a]pyridine (1.29 g) obtained in Example 43c).

NMR ($DMSO-d_6$) δ 2.83 (2H, t, J = 7.2 Hz), 2.92-3.06 (2H, m), 3.06-3.20 (2H, m), 3.55-3.78 (6H, m), 4.69 (2H, s), 6.95 (1H, d, J = 7.6 Hz), 7.65 (1H, d, J = 8.8 Hz), 7.73 (1H, dd, J = 8.8, 2.2 Hz), 7.90 (1H, dd, J = 8.8, 7.6 Hz), 8.01 (1H, dd, J = 8.8, 2.0 Hz), 8.18-8.32 (4H, m), 8.67 (1H, br), LC/MS 644 (M-HCl).

Example 44

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-ethoxycarbonylmethyl-imidazo[1,2-a]pyridine hydrochloride

44a) Ethyl 5-fluoroimidazo[1,2-a]pyridine-2-acetate

A solution of 2-amino-6-fluoropyridine (6.0 g) and ethyl 4-chloroacetoacetate (7.2 mL) in ethanol (120 mL) was refluxed for 12 hours. After cooling to room temperature, ethanol was distilled away under reduced pressure. To the residue was added saturated aqueous solution of sodium hydrogen carbonate (100 mL), and extracted with ethyl acetate (100 mL x 2). The extract was washed with saturated saline (100 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexane 2:1 → ethyl acetate/ethanol 20:1) to give the title compound 7.0 g (yield 71%) as a brown oil.

NMR ($CDCl_3$) δ 1.30 (3H, t, J = 7.0 Hz), 3.89 (2H, s), 4.22 (2H, q, J = 7.0 Hz), 6.42-6.48 (1H, m), 7.14-7.26 (1H, m), 740 (1H, dd, J = 9.2, 0.8 Hz), 7.67 (1H, s), LC/MS 233 (MH^+)

44b) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(ethoxycarbonylmethyl)imidazo[1,2-a]pyridine

A mixture of ethyl 5-fluoroimidazo[1,2-a]pyridine-2-acetate (6.4 g) obtained in Example 44a) and piperazine (10.0 g) was stirred at 100°C for 1 hour under a nitogen atmosphere. The reaction mixture was cooled to room temperature, and chloroform (200 mL) and water (200 mL)

were added thereto, followed by stirring well. The organic layer was separated, dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. To a solution of the residue in ethanol (70 mL) was added dropwise di-tert-butyl dicarbonate (6.6 mL) at room temperature, and stirred at room temperature for 30 minutes. Ethanol was distilled away under reduced pressure, and ethyl acetate (100 mL) and water (100 mL) were added. The organic layer was separated, and washed with saturated saline (100 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/ethanol 10:1) to give the title compound 5.5 g (yield 49%) as a pale yellow solid.

NMR ($CDCl_3$) δ 1.30 (3H, t, J = 7.2 Hz), 1.34 (9H, s), 3.08 (4H, t, J = 4.6 Hz), 3.68 (4H, bs), 3.88 (2H, s), 4.22 (2H, q, J = 7.2 Hz), 6.28 (1H, dd, J = 7.4, 1.0 Hz), 7.17 (1H, dd, J = 9.2, 7.4 Hz), 7.34 (1H, d, J = 9.2 Hz), 7.55 (1H, s), LC/MS 389 (MH^+)

44c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-ethoxycarbonylmethylimidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 36b), 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-

piperazinyl]-2-ethoxycarbonylmethylimidazo[1,2-a]pyridine was obtained as a colorless oil from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(ethoxycarbonylmethyl)imidazo[1,2-a]pyridine (1.5 g) obtained in Example 44b). This oil was dissolved in ethyl acetate (30 mL), and added 4M hydrogen chloride solution in ethyl acetate (1.0 mL), followed by stirring at room temperature for 10 minutes. The precipitate was collected by filtration, and washed sequentially with ethyl acetate, and diethyl ether, then dried under reduced pressure to give the title compound 1.2 g (yield 53%) as a white solid. NMR (DMSO-d_6) δ 1.24 (3H, t, J = 7.2 Hz), 2.83 (2H, t, J = 7.2 Hz), 3.00 (2H, bs), 3.12 (2H, bs), 3.61-3.70 (6H, m), 4.12 (2H, s), 4.17 (2H, q, J = 7.2 Hz), 6.96 (1H, d, J = 7.5 Hz), 7.65 (1H, d, J = 9.0 Hz), 7.73 (1H, dd, J = 8.7, 2.1 Hz), 7.90 (1H, dd, J = 8.7, 7.8 Hz), 8.00 (1H, dd, J = 8.4, 1.8 Hz), 8.11 (1H, s), 8.19 (1H, d, J = 8.4 Hz), 8.26-8.30 (2H, m), 8.67 (1H, d, J = 1.8 Hz), LC/MS 569 (MH^+).

Elemental analysis for $C_{28}H_{29}ClN_4O_5S \cdot HCl \cdot H_2O \cdot 0.5EtOAc$

Calcd (%): C, 53.97 ; H, 5.44 ; N, 8.39

Found (%): C, 54.24 ; H, 5.35 ; N, 8.21.

Example 45

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine

45a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]imidazo[1,2-

a]pyridine-2-acetic acid

To a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(ethoxycarbonylmethyl)imidazo[1,2-a]pyridine (3.5 g) obtained in Example 44b) in ethanol (50 mL) was added aqueous sodium hydroxide solution (8.0 M, 2.2 mL), and stirred at room temperature for 3 hours. Ethanol was distilled away under reduced pressure, and chloroform (100 mL) and saturated saline (100 mL) were added. Concentrated hydrochloric acid was slowly added thereto, and the aqueous layer was adjusted to pH 3. The organic layer was separated, dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure to give the title compound 3.3 g (yield 92%) as a brown solid. NMR ($CDCl_3$) δ 1.54 (9H, s), 3.10 (4H, t, J = 4.6 Hz), 3.70 (4H, bs), 4.02 (2H, s), 6.55 (1H, d, J = 7.4 Hz), 7.64-7.71 (3H, c), LC/MS 361 (MH^+)

45b) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine

To 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine-2-acetic acid (2.0 g) obtained in Example 45a) was added a solution of !.0M borane-THF complex in THF (16 mL), and stirred at room temperature for 1 hour. The reaction mixture was poured into ice-water (100 mL), and adjusted under ice-cooling to pH 1 with concentrated hydrochloric acid, followed by

stirring at room temperature for 1 hour. The reaction solution was adjusted to pH 11 with 1N aqueous sodium hydroxide solution, and extracted with ethyl acetate (50 mL x 2). The extract was dried over anhydrous magnesium sulfate, and solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/ethanol 4:1) to give the title compound 1.4 g (yield 80%) as a white solid.

NMR (DMSO) δ 1.44 (9H, s), 2.85 (2H, t, J = 7.1 Hz), 3.01 (4H, bs), 3.58 (4H, bs), 3.74 (2H, q, J = 6.5 Hz), 4.68 (1H, t, J = 5.4 Hz), 6.41 (1H, dd, J = 6.2, 2.0 Hz), 7.19-7.21 (2H, m), 7.54 (1H, s), LC/MS 347 (MH^+)

45c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine

According to a similar manner to Example 36b), the title compound 1.5 g (yield 62%) was obtained as a white crystal from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine (2.0 g) obtained in Example 45b).

NMR ($CDCl_3$) δ 2.96 (2H, t, J = 8.1 Hz), 3.04 (2H, t, J = 5.6 Hz), 3.13 (4H, bs,), 3.60 (2H, t, J = 8.1 Hz), 3.73 (4H, bs), 4.00 (2H, t, J = 5.6 H), 6.29 (1H, dd, J = 7.2, 0.9 Hz), 7.21 (1H, dd, J = 9.0, 7.2 Hz), 7.35-7.38 (2H, m,), 7.60 (1H, dd, J = 9.0,2.1 Hz), 7.61-7.95 (4H, m), 8.49 (1H, s), LC/MS 527 (MH^+).

Elemental analysis for $C_{26}H_{27}ClN_4O_4S \cdot 0.5H_2O$

Calcd (%): C, 58.26; H, 5.26; N, 10.45

Found (%): C, 58.09; H, 5.36; N, 10.18.

Example 46

5-[3-(Acetylamino)methyl-4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

46a) 5-[4-(tert-Butoxycarbonyl)-3-hydroxymethyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 37a), the title compound 3.6 g (yield 41%) was obtained as a brown powder from 5-(3-hydroxymethyl-1-piperazinyl)-2-methylimidazo[1,2-a]pyridine (6.2 g) obtained in Example 35a).

NMR ($CDCl_3$) δ1.51 (9H, s), 2.37 (3H, s), 2.61 (1H, br), 2.90-2.93 (1H, m), 3.29 (2H, d, J = 9.2 Hz), 3.64 (1H, d, J = 7.8 Hz), 3.88 (1H, br), 4.04-4.18 (3H, m), 4.33 (1H, m), 6.18 (1H, d, J = 7.2 Hz), 7.07-7.26 (3H, m).

46b) 5-[4-(tert-Butoxycarbonyl)-3-phthalimidomethyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

A solution of phthalimide (1.36 g), diisopropyl azodicarboxylate (4.68 g) and triphenylphosphine (2.42 g) in dichloromethane (90 mL) was was stirred at 0°C for 15 minutes, and added a solution of 5-[4-(tert-butoxycarbonyl)-3-hydroxymethyl-1-piperazinyl]-2-

methylimidazo[1,2-a]pyridine (0.80 g) obtained in Example 46a) in dichloromethane (10 mL), followed by stirring at 0°C for 2 hours, further at room temperature for 4 hours. The reaction solution was washed with aqueous sodium hydrogen carbonate solution, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 20:1) to give the title compound 0.65 g (yield 59%) as a brown oil.

NMR ($CDCl_3$) δ1.08 (9H, s), 2.50 (3H, s), 2.67 (1H, dt, J = 5.4 and 9.0 Hz), 3.10 (1H, dd, J = 3.0 and 12.0 Hz), 3.37-3.74 (4H, m), 3.96-4.90 (3H, m), 6.25 (1H, d, J = 6.9 Hz), 7.14 (1H, dd, J = 7.2 and 8.7 Hz), 7.31-7.87 (6H, m).

46c) 5-[3-(Acetylamino)methyl-4-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

A solution of 5-[4-(tert-butoxycarbonyl)-3-phthalimidomethyl-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.65 g) obtained in Example 46b) and hydrazine hydrate (0.25 mL) in ethanol (10 mL) was refluxed for 5 hours. The precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in THF (5 mL), and pyridine (1.5 mL) and acetic anhydride (0.5 mL) were added thereto, followed by stirring at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, diluted

with aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 5:1) to give the title compound 0.42 g (yield 79%) as a yellow oil.

NMR ($CDCl_3$) δ1.50 (9H, s), 1.99 (3H, s), 2.47 (3H, s), 2.69 (1H, dt, J = 3.0 and 12.0 Hz), 2.99 (1H, dd, J = 3.0 and 11.4 Hz), 3.20-3.50 (4H, m), 4.00-4.52 (3H, m), 5.90 (1H, br), 6.22 (1H, dd, J = 1.0 and 7.2 Hz), 7.12 (1H, dd, J = 6.9 and 9.0 Hz), 7.25-7.32 (2H, m).

46d) 5-[3-(Acetylamino)methyl-4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 37d), the title compound 0.21 g (yield 37%) was obtained as a colorless powder from 5-[3-(acetylamino)methyl-4-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.41 g) obtained in Example 46c).

NMR ($CDCl_3$) δ1.83-4.90 (19H, m), 5.93-6.46 (2H, m), 7.16-8.00 (8H, m), 8.48-8.53 (1H, m).

Elemental analysis for $C_{28}H_{30}ClN_5O_4S \cdot 1.3H_2O \cdot 0.3DMF$

Calcd (%): C, 56.59; H, 5.70; N, 12.10

Found (%): C, 56.41; H, 5.59; N, 12.37.

Example 47

5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(N'-ethylureidomethyl)imidazo[1,2-a]pyridine

47a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(N'-ethylureidomethyl)imidazo[1,2-a]pyridine

To a solution of 2-aminomethyl-5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine (2.76 g) obtained in Example 29b) in acetonitrile (25 mL) was added ethyl isocyanate (0.73 mL) at room temperature, and stirred at room temperature for 15 minutes. The deposited precipitate was collected by filtration, washed with acetonitrile (5 mL) and diethyl ether (5 mL), and dried under reduced pressure to give the title compound 2.88 g (yield 86%) as a white solid.

NMR ($CDCl_3$) δ 1.08 (3H, t, J = 7.0 Hz), 1.50 (9H, s), 2.98-3.12 (4H, m), 3.14-3.28 (2H, m), 3.57-3.78 (4H, m), 4.51 (2H, d, J = 6.0 Hz), 5.25 (1H, br), 5.90 (1H, br), 6.29 (1H, d, J = 7.2 Hz), 7.18 (1H, dd, J = 9.0, 7.2 Hz), 7.30 (1H, d, J = 9.0 Hz), 7.51 (1H, s).

47b) 2-(N'-Ethylureidomethyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

According to a similar manner to Example 1b), the title compound 1.67 g (yield 89%) was obtained from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(N'-ethylureidomethyl)imidazo[1,2-a]pyridine (2.01 g) obtained

in Example 47a).

NMR (D_2O) δ 1.11 (3H, t, J = 7.4 Hz), 3.17 (2H, q, J = 7.4 Hz), 3.46-3.57 (4H, m), 3.57-3.66 (4H, m), 4.58 (2H, s), 7.04 (1H, d, J = 7.4 Hz), 7.58 (1H, d, J = 9.2 Hz), 7.84-7.89 (2H, m).

47c) 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(N'-ethylureidomethyl)imidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.27 g (yield 87%) was obtained as a white solid from 2-(N'-ethylureidomethyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (1.13 g) obtained in Example 47b).

NMR ($CDCl_3$) δ 1.11 (3H, t, J = 7.4 Hz), 2.88-3.14 (6H, m), 3.14-3.30 (2H, m), 2.54-3.67 (2H, m), 3.67-3.89 (4H, m), 4.51 (2H, d, J = 5.8 Hz), 4.91 (1H, t, J = 5.6 Hz), 5.47 (1H, t, J = 5.8 Hz), 6.27 (1H, d, J = 7.2 Hz), 7.19 (1H, dd, J = 9.0, 7.2 Hz), 7.33 (1H, d, J = 9.0 Hz), 7.50 (1H, s), 7.61 (1H, dd, J = 8.8, 2.2 Hz), 7.90-7.99 (4H, m), 8.50 (1H, br), LC/MS 583 (M).

Example 48

5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-methyl-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine

48a) 5-[4-(tert-Butoxycarbonyl)-3-methyl-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine

A solution of 5-chloro-2-ethoxycarbonylimidazo[1,2-

a]pyridine (11.2 g) and 2-methylpiperazine (50.0 g) in acetonitrile (200 mL) was refluxed under an argon atmosphere for 72 hours. The solvent was distilled away under reduced pressure, water (250 mL) was added to the residue, and extracted with chloroform (250 mL). The extract was washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate and then the solvent was distilled away under reduced pressure. The residue was dissolved in ethanol (150 mL), and di-tert-butyl dicarbonate (10.9 g) was added dropwise at room temperature thereto, followed by stirring at room temperature for 1 hour. The solvent was distilled away under reduced pressure, water (200 mL) was added to the residue, and extracted with ethyl acetate (200 mL). The extract was washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate, and then solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexane 2:1) to give the title compound 15.0 g (yield 78%) as a colorless powder.

NMR ($CDCl_3$) δ 1.46-1.51 (15H, m), 2.68-2.87 (1H, m), 2.93-3.04 (1H, m), 3.18-3.30 (1H, m), 3.30-3.48 (2H, m), 4.01-4.15 (1H, m), 4.43-4.53 (3H, m), 6.36 (1H, d, J = 7.2 Hz), 7.26 (1H, dd, J = 9.2, 7.2 Hz), 7.43 (1H, d, J = 9.2 Hz), 8.23 (1H, s).

48b) 5-[4-(tert-Butoxycarbonyl)-3-methyl-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-3-methyl-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine (15.0 g) obtained in Example 48a) in ethanol (150 mL) was added 8N aqueous sodium hydroxide solution (9.7 mL), and stirred at room temperature for 30 minutes. The reaction solution was neutralized under ice-cooling with concentrated hydrochloric acid, and the solvent was distilled away under reduced pressure. The residue was diluted with water (50 mL), and adjusted under ice-cooling to pH 3-4 with concentrated hydrochloric acid, followed by extracting with chloroform (100 mL). The extract was dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. To the residue obtained was added a THF solution (100 mL) of 1.0M borane-THF complex, and stirred at room temperature for 1 hour under argon atmosphere. The reaction solution was poured into ice-water (300 mL), and adjusted to pH 1-2 with concentrated hydrochloric acid, followed by stirring at room temperature for 1 hour. The mixture was adjusted to pH 10-11 with 8N aqueous solution of sodium hydroxide, and extracted with ethyl acetate (150 mL). The extract was washed with saturated saline (100 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was

purified by silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/ethanol 10:1) to give the title compound 10.0 g (yield 76%) as a white solid.

NMR (DMSO-d_6) δ 1.36-1.44 (12H, m), 2.58-2.77 (1H, m), 2.81-2.94 (1H, m), 3.21-3.43 (3H, m), 3.82-3.97 (1H, m), 4.23-4.40 (1H, m), 4.61 (2H, d, J = 5.8 Hz), 5.22 (1H, t, J = 5.8 Hz), 6.40-6.44 (1H, m), 7.23-7.25 (2H, m), 7.62 (1H, s).

48c) 2-Hydroxymethyl-5-(3-methyl-1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

According to a similar manner to Example 13c), the title compound 5.43 g (yield 85.0%) was obtained as a white crystal from 5-[4-(tert-butoxycarbonyl)-3-methyl-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine (6.93 g) obtained in Example 48b).

NMR (D_2O) δ 1.49 (3H, d, J = 6.6 Hz), 3.08-3.26 (1H, m), 3.26-3.46 (1H, m), 3.52-3.79 (4H, m), 3.79-3.97 (1H, m), 4.95 (2H, s), 7.11 (1H, d, J = 7.6 Hz), 7.61 (1H, d, J = 8.8 Hz), 7.93 (1H, dd, J = 8.8, 7.6 Hz), 7.98 (1H, s).

48d) 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-methyl-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.07 g (yield 81%) was obtained as a white solid from 2-hydroxymethyl-5-(3-methyl-1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (1.04 g)

obtained in Example 48c).

NMR ($CDCl_3$) δ 1.36-1.66 (3H, m), 2.56-3.51 (7H, m), 3.60 (2H, t, J = 7.6 Hz), 3.69-3.89 (0.5H, m), 4.17-4.33 (0.5H, m), 4.46-4.59 (0.5H, m), 4.78-4.96 (0.5H, m), 4.88 (2H, s), 6.27 (1H, d, J = 7.2 Hz), 7.20 (1H, dd, J = 8.8, 7.2 Hz), 7.38 (1H, d, J = 8.8 Hz), 7.57 (1H, s), 7.61 (1H, dd, J = 8.8, 2.0 Hz), 7.91-8.00 (4H, m), 8.50 (1H, br), LC/MS 527 (M).

Example 49

5-[4-[3-[(1-tert-Butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]-2-(1-hydroxyethyl)imidazo[1,2-a]pyridine

According to a similar manner to Example 3e), the title compound 0.89 g (yield 72%) was obtained as a pale yellow powder from 2-(1-hydroxyethyl)-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (0.83 g) obtained in Example 24b).

NMR ($CDCl_3$) δ 1.64 (3H, d, J = 6.6 Hz), 1.74 (9H, s), 2.83-3.19 (6H, m), 3.35-3.59 (2H, m), 3.66-3.90 (2H, m), 4.01-4.15 (2H, m), 5.06 (1H, q, J =6.6 Hz), 6.33 (1H, d, J = 7.4 Hz), 7.24 (1H, dd, J = 8.8, 7.4 Hz), 7.33-7.54 (4H, m), 7.66-7.67 (1H, m), 7.92-8.02 (1H, m), LC/MS 616 (M).

Example 50

5-[4-[3-[(5-chloro-2-indolyl)sulfonyl]propionyl]piperazino]-2-(1-

hydroxyethyl)imidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 4, the title compound 0.37 g (yield 81%) was obtained as a white powder from 5-[4-[3-[(1-tert-butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionyl]piperazino]-2-(1-hydroxyethyl)imidazo[1,2-a]pyridine (0.51 g) obtained in Example 49).

NMR (DMSO-d_6) δ 1.55 (3H, d, J = 6.6 Hz), 2.84 (2H, t, J = 7.2 Hz), 2.93-3.07 (2H, m), 3.07-3.22 (2H, m), 3.22-3.58 (2H, m), 3.58-3.77 (4H, m), 5.07 (1H, dd, J = 6.6 Hz), 6.08 (1H, br), 6.99 (1H, d, J = 7.2 Hz), 7.18-7.19 (1H, m), 7.35 (1H, dd, J = 9.0, 2.2 Hz), 7.52-7.61 (2H, m), 7.81-7.98 (3H, m), LC/MS 516 (M-HCl).

Example 51

5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(dimethylcarbamoyl)methylimidazo[1,2-a]pyridine hydrochloride

51a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(dimethylcarbamoyl)methylimidazo[1,2-a]pyridine

To a solution of 2M dimethylamine THF solution (65 mL) and diisopropylethylamine (22.5 mL) in dichloromethane (100 mL) was added dropwise at 0°C a 1M solution of dimethylaluminium chloride in hexane (100 mL) under a nitrogen atmosphere, and stirred at the same temperature for 30 minutes. To this mixture was added dropwise at 0°C

a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(carboxymethyl)imidazo[1,2-a]pyridine (5.0 g) in dichlorometane (50 mL), and stirred at room temperature for 12 hours. The reaction mixture was poured into an ice-cooled saturated aqueous solution of sodium hydrogen carbonate, and extracted with chloroform (100 mL x 2). The extract was dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/ethanol 5:1 → 2:1) to give the title compound 3.45 g (yield 69%) as a pale yellow solid.

NMR ($CDCl_3$) δ 1.50 (9H, s), 2.99 (3H, s), 3.09 (4H, bs), 3.18 (3H, s), 3.66 (4H, bs), 3.93 (2H, s), 6.27 (1H, d, J = 7.0 Hz), 7.16 (1H, dd, J = 9.0, 7.0 Hz), 7.32 (1H, d, J = 9.0 Hz), 7.57 (1H, s), LC/MS 388 (MH^+)

51b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(dimethylcarbamoyl)methylimidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 44, the title compound 1.5 g (yield 67%) was obtained as a white solid from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(dimethylcarbamoyl)methylimidazo[1,2-a]pyridine (1.5 g) obtained in Example 51a).

NMR ($CDCl_3$) δ2.96 (2H, t, J = 7.5 Hz), 3.03 (3H, s), 3.13 (2H, bs), 3.24-3.26 (5H, m), 3.60 (2H, t, J = 7.5 Hz), 3.80

(4H, bs), 4.26 (2H, s), 6.74 (1H, d, J = 7.4 Hz), 7.59-7.66 (1H, m), 7.73 (1H, d, J = 7.4 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.93-8.00 (5H, m), 8.50 (1H, s), LC/MS 568 (MH^+).

Elemental analysis for $C_{28}H_{30}ClN_5O_4S \cdot HCl \cdot 0.5H_2O$

Calcd (%): C, 54.81; H, 5.26; N, 11.41

Found (%): C, 54.67; H, 5.18; N, 11.35.

Example 52

5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(methylcarbamoyl)methylimidazo[1,2-a]pyridine

52a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(methylcarbamoyl)methylimidazo[1,2-a]pyridine

To a solution of 2M methylamine THF solution (25 mL) and diisopropylethylamine (9.0 mL) in dichloromethane (50 mL) was added dropwise at 0°C a 1M solution of dimethylaluminium chloride in hexane (31 mL) under a nitrogen atmosphere, and stirred at the same temperature for 30 minutes. To this mixture was added dropwise at 0°C a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(carbethoxymethyl)imidazo[1,2-a]pyridine (2.0 g) in dichlorometane (20 mL), and stirred at room temperature for 12 hours. The reaction mixture was poured into an ice-cooled saturated aqueous solution of sodium hydrogen carbonate, and extracted with chloroform (100 mL x 2). The extract was dried over anhydrous magnesium sulfate, and the

solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 5:1 → 2:1) to give the title compound 1.44 g (yield 75%) as a pale yellow solid.

NMR ($CDCl_3$) δ 1.51 (9H, s), 2.82 (3H, s), 3.07 (4H, bs), 3.68 (4H, bs), 3.75 (2H, s), 6.33 (1H, dd, J = 7.4, 1.2 Hz), 7.19-7.44 (3H, c), LC/MS 374 (MH^+)

52b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(methylcarbamoyl)methylimidazo[1,2-a]pyridine

According to a similar manner to Example 36, the title compound 0.59 g (yield 74%) was obtained as a white crystal from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(methylcarbamoyl)methylimidazo[1,2-a]pyridine (0.69 g) obtained in Example 52a).

NMR ($CDCl_3$) δ 2.82 and 2.80 (3H, s), 2.93-3.15 (8H, m), 3.60 (2H, t, J = 6.4 Hz), 3.75-3.82 (4H, m), 6.42 (1H, dd, J = 7.0, 1.2 Hz), 7.32-7.64 (5H, m), 7.64-8.00 (4H, m), 8.50 (1H, s), LC/MS 554 (MH^+).

Elemental analysis for $C_{27}H_{28}ClN_5O_4S \cdot H_2O$

Calcd (%): C, 56.69; H, 5.29; N, 12.24

Found (%): C, 56.59; H, 5.18; N, 12.11.

Example 53

5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(carbamoyl)methylimidazo[1,2-a]pyridine

53a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(carbamoyl)methylimidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(carboxymethyl)imidazo[1,2-a]pyridine (2.5 g) in acetonitrile (100 mL) was added 25% ammonia solution (100 mL), and stirred at 50°C for 24 hours. The acetonitrile was distilled away under reduced pressure, and extracted with chloroform (50 mL x 2). The extract was dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 2:1) to give the title compound 1.95 g (yield 78%) as a white solid.

NMR ($CDCl_3$) δ 1.51 (9H, s), 3.08 (4H, t, J = 4.8 Hz), 3.68 (4H, bs), 3.76 (2H, s), 5.31 (1H, s), 5.48 (1H, bs), 6.33 (1H, dd, J = 7.0, 1.0 Hz), 7.23 (1H, dd, J = 8.8, 7.0 Hz), 7.34 (1H, d, J = 8.8 Hz), 7.46 (1H, s), LC/MS 360 (MH^+).

53b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(carbamoyl)methylimidazo[1,2-a]pyridine

According to a similar manner to Example 36b), the title compound 0.59 g (yield 62%) was obtained as a white crystal from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(carbamoyl)methylimidazo[1,2-a]pyridine (0.91 g) obtained in Example 53a).

NMR ($CDCl_3$) δ2.93-3.12 (6H, m), 3.60 (2H, t, J = 7.4 Hz),

3.77-3.81 (6H, m), 5.47 (2H, bs), 6.31 (1H, dd, J = 7.0, 1.2 Hz), 7.25 (1H, dd, J = 8.8, 7.0 Hz), 7.37 (1H, d, J = 8.8 Hz), 7.45 (1H, s), 7.61 (1H, dd, J = 8.8, 2.2 Hz), 7.94-8.00 (4H, m), 8.50 (1H, s), LC/MS 540 (MH^+).

Elemental analysis for $C_{26}H_{26}ClN_5O_4S \cdot H_2O$

Calcd (%): C, 55.96; H, 5.06; N, 12.55

Found (%): C, 56.09; H, 4.90; N, 12.71.

Example 54

5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-(carbamoyloxy)ethyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

54a) 5-[4-(tert-Butoxycarbonyl)-3-[2-(carbamoyloxy)ethyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

5-[4-(tert-Butoxycarbonyl)-3-(2-hydroxyethyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.36 g) obtained in Example 41a) was dissolved in dichloromethane (10 mL), and added trichloroacetyl isocyanate (0.18 mL) with cooling to 0°C, followed by stirring at 0°C for 1 hour. Methanol (5 mL) and water (5 mL) were added thereto, further added potassium carbonate (0.42 g), and stirred at 0°C for 3 hours. The reaction solution was concentrated under reduced pressure, and diluted with water, followed by extracting with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the title compound 0.43 g (quantitative)

as a colorless powder.

NMR ($CDCl_3$) δ 1.50 (9H, s), 1.95-4.63 (16H, m), 6.24 (1H, d, J = 7.0 Hz), 7.13 (1H, dd, J = 7.0 and 9.0 Hz), 7.26-7.33 (2H, m).

54b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-(carbamoyloxy)ethyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 37, the title compound was obtained as a a colorless powder 0.20 g (yield 34%) from 5-[4-(tert-butoxycarbonyl)-3-[2-(carbamoyloxy)ethyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.40 g) obtained in Example 54a).

NMR ($CDCl_3$) δ2.11-4.94 (20H, m), 6.21-6.24 (1H, m), 7.13 (1H, dd, J = 7.5 and 9.0 Hz), 7.25-8.48 (8H, m).

Elemental analysis for $C_{28}H_{30}ClN_5O_5S \cdot 0.7H_2O \cdot 0.6Et_2O$

Calcd (%): C, 56.95 ; H, 5.88 ; N, 10.92

Found (%): C, 57.05 ; H, 5.72 ; N, 10.61.

Example 55

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-(methylthio)ethyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

55a) 5-[4-(tert-Butoxycarbonyl)-3-[2-(methanesulfonyloxy)ethyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-3-(2-

hydroxyethyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.50 g) obtained in Example 41a) and triethylamine (0.28 g) in THF (5 mL) was added methanesulfonyl chloride (0.16 mL) with cooling to 0°C, and stirred at room temperature for 2 hours. The reaction solution was diluted with aqueous sodium carbonate solution, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the title compound 0.61 g (quantitative) as a colorless powder.

NMR ($CDCl_3$) δ1.51 (9H, s), 2.13-4.55 (17H, m), 6.24 (1H, d, J = 6.6 Hz), 7.13 (1H, dd, J = 7.2 and 9.0 Hz), 7.26-7.33 (2H, m).

55b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-(methylthio)ethyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-3-[2-(methanesulfonyloxy)ethyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (1.25 g) obtained in Example 55a) in DMF (10 mL) was added 15% aqueous solution of methylmercaptan sodium (1.7 mL), and stirred at room temperature for 15 hours. The reaction solution was diluted with aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and concentrated under

reduced pressure. The residue was dissolved in concentrated hydrochloric acid (2 mL), and stirred at room temperature for 10 minutes. The reaction solution was concentrated under reduced pressure, then, subjected to azeotropy with ethanol, and the residue was washed with isopropanol. The white powder obtained and DBU (0.61 g) were dissolved in DMF (3 mL), and this solution was added to a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoic acid (0.60 g), HOBt (0.46 g) and WSC (0.58 g) in DMF (10 mL), followed by stirring at room temperature for 4 hours. The reaction solution was concentrated under reduced pressure, diluted with aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate and THF. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (ethyl acetate) to give the title compound 0.50 g (yield 31%) as a colorless powder.

NMR ($CDCl_3$) δ1.99-4.89 (21H, m), 6.20 (1H, d, J = 7.2 Hz), 7.13 (1H, dd, J = 7.5 and 8.7 Hz), 7.26-8.50 (8H, m).

Elemental analysis for $C_{28}H_{31}ClN_4O_3S_2 \cdot 0.9H_2O$

Calcd (%): C, 57.26; H, 5.63; N, 9.54

Found (%): C, 57.65; H, 5.69; N, 9.16.

Example 56

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-

(methylsulfinyl)ethyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-(methylthio)ethyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.45 g) obtained in Example 55c) and methanesulfonic acid (0.10 mL) were dissolved in dichloromethane (7 mL), and a solution of 3-chloroperbenzoic acid (70%; 0.19 g) in dichloromethane (3 mL) was added dropwise at 0°C, followed by stirring at room temperature for 1 hour. To the reaction solution was added saturated aqueous solution of sodium thiosulfate, and stirred at room temperature for 1 hour. The reaction solution was diluted with aqueous solution of sodium hydrogen carbonate, and organic layer was separated. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 20:1) to give the title compound 210 mg (yield 45%) as a colorless powder.

NMR ($CDCl_3$) δ2.15-5.00 (21H, m), 6.22 (1H, d, J = 7.0 Hz), 7.14 (1H, dd, J = 7.4 and 9.0 Hz), 7.33-7.36 (2H, m), 7.61 (1H, dd, J = 1.8 and 9.2 Hz), 7.90-8.00 (4H, m), 8.51 (1H. s).

Elemental analysis for $C_{28}H_{31}ClN_4O_4S_2 \cdot 1.5H_2O \cdot 0.3EtOAc$

Calcd (%): C, 54.75 ; H, 5.73 ; N, 8.75

Found (%): C, 54.73; H, 5.68; N, 8.43.

Example 57

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-(methylsulfonyl)ethyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-[2-(methylthio)ethyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.45 g) obtained in Example 55c) and methanesulfonic acid (0.10 mL) were dissolved in dichloromethane (7 mL), and a solution of 3-chloroperbenzoic acid (70%; 0.19 g) in dichloromethane (3 mL) was added dropwise at 0°C, followed by stirring at room temperature for 1 hour. To the reaction solution was added saturated aqueous solution of sodium thiosulfate, and stirred at room temperature for 1 hour. The reaction solution was diluted with aqueous solution of sodium hydrogen carbonate, and organic layer was separated. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 20:1) to give the title compound 0.16 g (yield 34%) as a colorless powder. NMR ($CDCl_3$) δ2.14-5.01 (21H, m), 6.23 (1H, d, J = 6.2 Hz), 7.14 (1H, dd, J = 7.0 and 9.0 Hz), 7.31-7.37 (2H, m), 7.61 (1H, dd, J = 1.8 and 8.6 Hz), 7.91-8.01 (4H, m), 8.51 (1H.

s).

Elemental analysis for $C_{28}H_{31}ClN_4O_5S_2 \cdot 0.7H_2O \cdot 0.2EtOAc$

Calcd (%): C, 54.61; H, 5.41; N, 8.85

Found (%): C, 54.93; H, 5.58; N, 8.80.

Example 58

5-[4-[3-[(1-tert-Butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine

5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine (1.1 g) obtained in Example 45b) was dissolved by adding concentrated hydrochloric acid (5 mL). To this solution was added ethanol (50 mL), and concentrated under reduced pressure. To the residue was added again ethanol, and concentrated again under reduced pressure. To the residue was added isopropyl alcohol, and the precipitate was collected by filtration. The solid was washed sequentially with isopropyl alcohol, and diethyl ether, and dried under reduced pressure to give 5-(1-piperazinyl)-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine dihydrochloride as a white solid. 3-[(1-tert-Butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionic acid (1.0 g) was suspended in acetonitrile (50 mL), and $HOBt \cdot H_2O$ (0.66 g) and WSC (0.75 g) were added sequentially, followed by stirring at at room temperature for 20 minutes. To this reaction solution was

added a solution of 5-(1-piperazinyl)-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine dihydrochloride previously obtained, DBU (936 mL) and triethylamine (1.1 mL) in acetonitrile (20 mL), and stirred at at room temperature for 2 hours. The acetonitrile was distilled away under reduced pressure, and to the residue were added chloroform (100 mL) and water (100 mL). The organic layer was separated, washed with saturated saline (100 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 3:1), and recrystallized from ethyl acetate/ethanol to give the title compound 0.67 g (yield 35%) as a white crystal.

NMR ($CDCl_3$) δ 1.75 (9H, s), 2.98-3.13 (8H, m), 3.73 (4H, bs), 4.02 (2H, t, J = 5.7 Hz), 4.11 (2H, t, J = 7.7 Hz), 6.32 (1H, d, J = 6.6 Hz), 7.21-7.26 (1H, m), 7.37-7.41 (4H, m), 7.45 (1H, dd, J = 9.0, 2.1 Hz), 7.52 (1H, s), 7.65 (1H, d, J = 2.1 Hz), 7.99 (1H, d, J = 9.0 Hz), LC/MS 616 (MH^+),

Elemental analysis for $C_{29}H_{34}ClN_5O_6S \cdot 1.5H_2O$

Calcd (%): C, 54.16; H, 5.80; N, 10.89

Found (%): C, 54.02; H, 5.63; N, 10.68.

Example 59

5-[4-[3-[(5-Chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine

hydrochloride

According to a similar manner to Example 4, the title compound 0.39 g (yield 86%) was obtained as a a white solid from 5-[4-[3-[(1-tert-butoxycarbonyl-5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine (0.5 g) obtained in Example 58.

NMR (DMSO-d_6) δ 2.83 (2H, t, J = 6.6 Hz), 3.00 (4H, t, J = 5.4 Hz), 3.13 (2H, bs), 3.62 (2H, bs), 3.70 (4H, t, J = 7.1 Hz), 3.79 (2H, t, J = 6.6 Hz), 5.74 (1H, d, J = 0.9 Hz), 6.95 (1H, d, J = 7.8 Hz), 7.17 (1H, s), 7.34 (1H, d, J = 8.7 Hz), 7.53 (1H, d, J = 9.0 Hz), 7.60 (1H, d, J = 9.0 Hz), 7.80 (1H, s), 7.87 (1H, dd, J = 8.7, 7.8 Hz) 7.99 (1H, s),

LC/MS 516 (MH^+),

Elemental analysis for $C_{24}H_{26}ClN_5O_4S \cdot HCl \cdot 2H_2O$

Calcd (%): C, 48.98; H, 5.31; N, 11.90

Found (%): C, 48.87; H, 5.32; N, 11.45.

Example 60

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-carbamoyl-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine

60a) 5-[3-(Carbamoyl)-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine

A solution of 2-piperazinecarboxamide (17.3 g) and 2-ethoxycarbonyl-5-chloroimidazo[1,2-a]pyridine (10.0 g) in

acetonitrile (100 mL) was stirred at 120°C for 15 hours. The reaction mixture was diluted with chloroform and water, and the precipitate was collected by filtration, followed by washing with water to give the title compound 4.87 g (yield 35%) as a white powder.

NMR (DMSO-d_6) δ1.33 (3H, t, J = 7.2 Hz), 2.79-3.10 (6H, m), 3.42-3.53 (2H, m), 4.31 (2H, q, J = 7.2 Hz), 6.51-6.54 (1H, m), 7.31-7.36 (3H, m), 7.50 (1H, s), 8.71 (1H, s).

60b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-3-carbamoyl-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine

To a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoic acid (0.45 g) obtained in Example 60a), WSC (0.43 g) and HOBt (0.35 g) in DMF (30 mL) was added 5-[3-(carbamoyl)-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine (0.48 g) obtained in Example 60a), and stirred at room temperature for 3 days. The reaction solution was concentrated under reduced pressure, diluted with aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate and THF. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue obtained was purified by basic silica gel column chromatography (eluent: THF), and crystallized from ethyl acetate to give the title compound 0.40 g (yield 45%) as a

white powder.

NMR ($CDCl_3$) δ1.46 (3H, t, J = 7.2 Hz), 2.65 (1H, dd, J = 4.0 and 12.0 Hz), 2.82-3.08 (2H, m), 3.32-3.53 (3H, m), 3.76-3.93 (2H, m), 4.13-4.19 (2H, m), 4.36 (1H, d, J = 12.0 Hz), 4.48 (2H, q, J = 6.0 Hz), 5.44 (1H, s), 5.93 (1H, s), 6.32 (1H, d, J = 6.6 Hz), 6.82 (1H, s), 7.19-7.25 (1H, m), 7.48 (1H, d, J = 9.0 Hz), 7.61 (1H, dd, J = 1.8 and 8.7 Hz), 7.90-7.99 (4H, m), 8.49 (1H, s), 9.02 (1H, s).

Elemental analysis for $C_{28}H_{28}ClN_5O_6S \cdot 0.5H_2O \cdot 0.3EtOAc$

Calcd (%): C, 55.36; H, 5.00; N, 11.05

Found (%): C, 55.42; H, 4.86; N, 10.87.

Example 61

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxy-2-methylpropyl)imidazo[1,2-a]pyridine hydrochloride

61a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(2-hydroxy-2-methylpropyl)imidazo[1,2-a]pyridine

A 1M solution of methylmagnesium bromide in THF (22 mL) was added dropwise at 0°C to a suspension of cerium chloride (5.72 g) in THF (30 mL) that was srirred vigorously at room temperature under a nitrogen atmosphere for 12 hours, and stirred at the same temperature for 2.5 hours. To this suspension was added a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(ethoxycarbonylmethyl)imidazo[1,2-a]pyridine (1.6 g)

obtained in Example 44b) in THF (100 mL), and stirred at 0°C for 2 hours. The reaction mixture was poured into ice-cooled 5% aqueous acetic acid solution, and extracted with ethyl acetate (50 mL x 3). The extract was washed with saturated saline (100 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/ethanol 2:1). The crude product obtained was again subjected to the similar reaction with cerium chloride (6.64 g) and 1M solution of methylmagnesium bromide in THF (44 mL). Being post-treated and purified similarly, the title compound 0.22 g (yield 14%) was obtained as a pale yellow solid.

NMR ($CDCl_3$) δ 1.26 (6H, s), 1.51 (9H, s), 2.92 (2H, s), 3.08 (4H, t, J = 5.0 Hz), 3.69 (4H, bs), 6.30 (1H, dd, J = 7.4, 0.9 Hz), 7.15-7.23 (2H, m), 7.31-7.34 (2H, m), LC/MS 375 (MH^+)

61b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxy-2-methylpropyl)imidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 44b), the title compound 0.14 g (yield 50%) was obtained as a a white solid from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(2-hydroxy-2-methylpropyl)imidazo[1,2-a]pyridine (0.22 g)

obtained in Example 61a).

NMR (DMSO-d_6) δ 1.20 (6H, s), 2.82 (2H, t, J = 7.3 Hz), 2.94 (2H, s), 3.01 (2H, bs), 3.12 (2H, bs), 3.64-3.68 (6H, m), 6.95 (1H, d, J = 7.6 Hz), 7.63 (1H, d, J = 8.8 Hz), 7.74 (1H, dd, J = 8.4, 2.2 Hz), 7.88 (1H, dd, J = 8.8, 7.6 Hz), 7.96 (1H, s), 8.02 (1H, dd, J = 8.4, 1.4 Hz), 8.21 (1H, d, J = 8.4 Hz), 8.28-8.32 (2H, m), 8.69 (1H, s), LC/MS 555 (MH^+),

Elemental analysis for $C_{28}H_{31}ClN_4O_4S \cdot HCl \cdot 2H_2O$

Calcd (%): C, 53.59; H, 5.78; N, 8.93

Found (%): C, 53.72; H, 5.80; N, 8.72.

Example 62

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(1H-tetrazol-5-yl)methylimidazo[1,2-a]pyridine trifluoroacetate

62a) 5-[4-(tert-Butoxycarbonyl-1-piperazinyl]-2-cyanomethylimidazo[1,2-a]pyridine

Cyanuric chloride (0.50 g) was added to a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(carbamoyl)methylimidazo[1,2-a]pyridine (1.95 g) obtained in Example 53a) in dimethylformanide (6 mL), and stirred at room temperature for 1 hour. Further, cyanuric chloride (0.50 g) was added to the reaction solution, and stirred at room temperature for 12 hours. Under ice-cooling, to the reaction solution were added saturated aqueous solution of

sodium hydrogen carbonate (50 mL) and ethyl acetate (50 mL). The organic layer was washed with saturated saline (50 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate) to give the title compound 0.47 g (yield 25%) as a yellow oil.

NMR ($CDCl_3$) δ 1.51 (9H, s), 3.08 (4H, t, J = 4.7 Hz), 3.69 (4H, bs), 3.96 (2H, s), 6.35 (1H, dd, J = 6.9, 1.4 Hz), 7.20-7.37 (2H, m), 7.59 (1H, s), LC/MS 342 (MH^+).

62b) 5-[4-(tert-Butoxycarbonyl-1-piperazinyl]-2-(1H-tetrazol-5-yl)methylimidazo[1,2-a]pyridine

Trimethyltin azide (0.43 g) was added to a solution of 5-[4-(tert-butoxycarbonyl-1-piperazinyl]-2-cyanomethylimidazo[1,2-a]pyridine (0.47 g) obtained in Example 62a) in toluene, and refluxed under an argon atmosphere for12 hours. The toluene was distilled away under reduced pressure, and the residue was dissolved in methanol, and concentrated again under reduced pressure. To the residue was added diethyl ether, and the precipitate was collected by filtration to give the title compound 0.68 g (quantitative) as a pale brown solid.

NMR ($CDCl_3$) δ 1.49 (9H, s), 3.06 (4H, bs), 3.66 (4H, bs), 4.50 (2H, s), 6.37 (1H, d, J = 2.6 Hz), 7.21-7.27 (1H, m), 7.38 (1H, d, J = 8.8 Hz), 7.51 (1H, s), LC/MS 385 (MH^+)

62c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(1H-tetrazol-5-yl)methylimidazo[1,2-a]pyridine trifluoroacetate

To a solution of 5-[4-(tert-butoxycarbonyl-1-piperazinyl]-2-(1H-tetrazol-5-yl)methylimidazo[1,2-a]pyridine (0.68 g) obtained in Example 62b) in ethyl acetate (5 mL) was added a 4N solution of hydrogen chloride in ethyl acetate (30 mL), and stirred at room temperature for 2 hours. The precipitate was collected by filtration, washed with diethyl ether, and dried under reduced pressure to give 5-(1-piperazinyl)-2-(1H-tetrazol-5-yl)methylimidazo[1,2-a]pyridine dihydrochloride as a white solid. The obtained 5-(1-piperazinyl)-2-(1H-tetrazol-5-yl)methylimidazo[1,2-a]pyridine dihydrochloride was suspended in acetonitrile (5 mL), and DBU (126 mL) and N-trimethylsilylacetamide (0.18 g) were sequentially added thereto, followed by stirring at room temperature for 1 hour. This solution was added to a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoic acid (0.53 g) obtained in Example 60a), WSC (0.51 g) and HOBt (0.41 g) in DMF (30 mL), and stirred at room temperature for 3 hours. The acetonitrile was distilled away under reduced pressure, and to the residue were added chloroform (30 mL) and water (30 mL). To the aqueous layer was added 1N hydrochloric acid and adjusted to pH 3. The organic layer was separated,

washed with saturated saline (30 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by preparative HPLC, and the solvent was distilled away under reduced pressure to give the title compound 86 mg (yield 45%) as a white solid.

NMR (DMSO-d_6) δ 2.82 (2H, t, J = 2.5 Hz), 2.86 (2H, bs), 3.12 (2H, bs), 3.36-3.68 (6H, m), 4.62 (2H, s), 6.86 (1H, d, J = 7.4 Hz), 7.56 (1H, d, J = 9.2 Hz), 7.73-7.79 (2H, m), 8.00 (1H, dd, J = 8.5, 1.9 Hz), 8.12-8.32 (4H, m), 8.68 (1H, s), LC/MS 565 (MH^+),

Elemental analysis for $C_{26}H_{25}ClN_8O_3S \cdot CF_3COOH \cdot H_2O$

Calcd (%): C, 48.24; H, 4.05; N, 16.07

Found (%): C, 48.09; H, 4.16, N, 15.80.

Example 63

5-[4-[3-[(6-Bromo-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine

To a solution of 3-[(6-bromo-2-naphthyl)sulfonyl]propanoic acid (0.17 g), WSC (0.14 g) and HOBt (0.12 g) in acetonitrile (20 mL) was added a solution of 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine hydrochloride (0.14 g) obtained in Example 1b), DBU (0.15 g) and triethylamine (0.15 g) in acetonitrile (10 mL), and stirred at room temperature for 15 hours. The reaction solution was

concentrated under reduced pressure, diluted with aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate and THF. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue obtaind was crystallized from ethyl acetate-methanol to give the title compound 92 mg (yield 35%) as a white powder.

NMR ($CDCl_3$) δ2.96 (2H, t, J = 7.8 Hz), 3.05-3.13 (4H, m), 3.59 (2H, t, J = 7.8 Hz), 3.62-3.80 (4H, m), 6.28 (1H, dd, J = 0.9 and 7.2 Hz), 7.19 (1H, dd, J = 7.2 and 9.0 Hz), 7.44 (1H, d, J = 9.0 Hz), 7.54 (1H, t, J = 0.9 Hz), 7.66 (1H, d, J = 1.2 Hz), 7.73 (1H, dd, J = 8.7 and 1.8 Hz), 7.84-7.97 (3H, m), 8.13 (1H, d, J = 1.8 Hz), 8.48 (1H, d, J = 0.6 Hz).

Elemental analysis for $C_{24}H_{23}BrN_4O_3S \cdot 0.8H_2O$

Calcd (%): C, 53.20 ; H, 4.58 ; N, 10.34

Found (%): C, 53.24 ; H, 4.37 ; N, 10.00.

Example 64

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxypropyl)imidazo[1,2-a]pyridine

64a) 5-[4-(tert-Butoxycarbonyl-1-piperazinyl]-2-(2-oxopropyl)imidazo[1,2-a]pyridine

To a suspension of cerium chloride (5.72 g) in THF (30 mL) that was srirred vigorously at room temperature for 12 hours under a nitrogen atmosphere was added 5-[4-(tert-

butoxycarbonyl)-1-piperazinyl]-2-(dimethylcarbamoyl)methylimidazo[1,2-a]pyridine (3.0 g) obtained in Example 51a), and srirred for 1 hour. To this mixture was added dropwise at 0°C a 1M solution of methylmagnesium bromide in THF (124 mL), and stirred at the same temperature for 1 hour. The reaction mixture was poured into ice-cooled 5% aqueous acetic acid solution, and extracted with ethyl acetate (50 mL x 3). The extract was washed with saturated saline (100 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/ethanol 2:1) to give the title compound 1.9 g (yield 69%) as a yellow oil.

NMR ($CDCl_3$) δ 1.50 (9H, s), 2.29 (3H, s), 3.07 (4H, bs), 3.67 (4H, bs), 3.94 (2H, s), 6.29 (1H, dd, J = 7.2, 0.9 Hz), 7.18 (1H, dd, J = 9.0, 7.2 Hz), 7.35 (1H, d, J = 9.0 Hz), 7.48 (1H, s), LC/MS 359 (MH^+)

64b) 5-[4-(tert-Butoxycarbonyl-1-piperazinyl]-2-(2-hydroxypropyl)imidazo[1,2-a]pyridine

Sodium borohydride (0.35 g) was added under ice-cooling to a solution of 5-[4-(tert-butoxycarbonyl-1-piperazinyl]-2-(2-oxopropyl)imidazo[1,2-a]pyridine (1.1 g) obtained in Example 64a) in ethanol (20 mL), and srirred at room temperature for 1 hour. To the reaction solution was

added water (5 mL), and ethanol was distilled away under reduced pressure. To the residue were added ethyl acetate (50 mL) and water (50 mL), and srirred well. The organic layer was separated, washed with saturated saline (50 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 5:1) to give the title compound 0.88 g (yield 79%) as a yellow oil.

NMR ($CDCl_3$) δ 1.30 (3H, d, J = 6.2 Hz,), 1.51 (9H, s), 2.79 (1H, dd, J = 14.6, 8.4 Hz), 2.97 (1H, dd, J = 14.6, 3.4 Hz), 3.05-3.10 (4H, m), 3.67-3.78 (4H, m), 4.14-4.24 (1H, m), 6.29 (1H, d, J = 7.0), 7.18 (1H, dd, J = 8.8, 7.0 Hz), 7.28-7.35 (2H, m), LC/MS 361 (MH^+)

64c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxypropyl)imidazo[1,2-a]pyridine

According to a similar manner to Example 36b), the title compound 0.72 g (yield 73%) was obtained as a a white crystal from 5-[4-(tert-butoxycarbonyl-1-piperazinyl]-2-(2-hydroxypropyl)imidazo[1,2-a]pyridine (0.88 g) obtained in Example 64b).

NMR ($CDCl_3$) δ 1.30 (3H, d, J = 6.3 Hz), 2.80 (1H, dd, J = 14.7, 8.7 Hz), 2.94-2.99 (3H, m), 3.08 (4H, d, J = 26.1 Hz), 3.60 (2H, t, J = 7.2 Hz), 3.73 (4H, bs), 4.17-4.23 (1H, m), 6.26 (1H, d, J = 7.2 Hz), 7.18 (1H, dd, J = 8.7, 7.2 Hz),

7.33-7.35 (2H, m), 7.59 (1H, dd, J = 8.7, 2.0 Hz), 7.90-7.96 (4H, m), 8.49 (1H, s), LC/MS 541 (MH^+),

Elemental analysis for $C_{27}H_{29}ClN_4O_4S \cdot 0.5H_2O$

Calcd (%): C, 58.95; H, 5.50; N, 10.19

Found (%): C, 59.25; H, 5.78; N, 9.83.

Example 65

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl]imidazo[1,2-a]pyridine hydrochloride

65a) 5-[4-(tert-Butoxycarbonyl-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl]imidazo[1,2-a]pyridine

5-Chloroimidazo[1,2-a]pyridine (3.74 g) and homopiperazine (24.6 g) were mixed, and srirred at 125°C for 18 hours under an argon atmosphere. To the solid obtained were added water (200 mL) and chloroform (200 mL), organic layer was separated, and washed with saturated saline (200 mL), followed by drying over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, the residue obtained was dissolved in ethanol (100 mL), di-tert-butyl dicarbonate (5.36 g) was added dropwise at room temperature thereto, and the reaction solution was stirred at room temperature for 1 hour. The solvent was distilled away under reduced pressure, water (200 mL) was added to the residue, and extracted with ethyl acetate (200 mL). The extract was

washed with saturated saline (200 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 10:1) to give the title compound 7.30 g (yield 94%) as a pale yellow powder.

NMR ($CDCl_3$) δ 1.50 (9H, s), 1.97-2.14 (2H, m), 3.18-3.36 (4H, m), 3.57-3.76 (4H, m), 6.34 (1H, d, J = 7.2 Hz), 7.15 (1H, dd, J = 8.7, 7.2 Hz), 7.37 (1H, d, J = 8.7 Hz), 7.58-7.63 (2H, m).

65b) 5-(2,3,5,6-Tetrahydro-7H-1,4-diazepin-1-yl)imidazo[1,2-a]pyridine dihydrochloride

5-[4-(tert-Butoxycarbonyl-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl]imidazo[1,2-a]pyridine (7.30 g) obtained in Example 65a) was added to concentrated hydrochloric acid (19.0 mL), and srirred at room temperature for 20 minutes. To the reaction solution was added ethanol (75 mL), and concentrated under reduced pressure. To the residue was added ethanol-ether, and the formed precipitate was collected by filtration. The solid was washed with ethanol (10 mL) and diethyl ether (10 mL), and dried under reduced pressure to give the title compound 5.48 g (yield 82%) as a white powder.

NMR (D_2O) δ 2.28-2.42 (2H, m), 3.49-3.60 (2H, m), 3.60-3.72 (4H, m), 3.76-3.87 (2H, m), 7.14 (1H, d, J = 7.5 Hz), 7.63

(1H, d, J = 8.7 Hz), 7.89-7.99 (3H, m).

65c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl]imidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.12 g (yield 90%) was obtained as a a colorless powder from 5-(2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)imidazo[1,2-a]pyridine dihydrochloride (0.87 g) obtained in Example 65b).

NMR ($CDCl_3$) δ 1.58-1.83 (1H, m), 2.02-2.22 (2H, m), 2.89-3.03 (2H, m), 3.17-3.28 (3H, m), 3.37-3.44 (1H, m), 3.57-3.68 (2H, m), 3.68-3.85 (3H, m), 6.25-6.34 (1H, m), 7.12-7.18 (1H, m), 7.37-7.42 (1H, m), 7.51 (1H, s), 7.58 (1H, dd, J = 8.7, 2.0 Hz), 7.63-7.65 (1H, m), 7.91-7.96 (4H, m), 8.47-8.48 (1H, m).

65d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl]imidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 1d), the title compound 1.16 g (yield 89%) was obtained as a a white powder from 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl]imidazo[1,2-a]pyridine (1.22 g) obtained in Example 65c).

NMR (DMSO-d_6) δ 1.36-1.78 (1H, m), 1.83-2.12 (2H, m), 2.70-

2.89 (3H, m), 3.12-3.32 (2H, m), 3.32-3.57 (2H, m), 3.57-3.78 (4H, m), 6.96-7.04 (1H, m), 7.59-7.75 (2H, m), 7.84-8.03 (3H, m), 8.16-8.29 (4H, m), 8.66 (1H, br), LC/MS 497 (M-HCl).

Example 66

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl]-2-methylimidazo[1,2-a]pyridine dihydrochloride

66a) 5-[4-(tert-Butoxycarbonyl-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl]-2-methylimidazo[1,2-a]pyridine

2-Methyl-5-chloroimidazo[1,2-a]pyridine (4.13 g) and homopiperazine (24.80 g) were mixed, and srirred at 125°C for 42 hours under an argon atmosphere. To the solid obtained were added water (200 mL) and chloroform (200 mL), organic layer was separated, and washed with saturated saline (200 mL). The organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue obtained was dissolved in ethanol (100 mL), di-tert-butyl dicarbonate (5.41 g) was added dropwise at room temperature thereto, and the reaction solution was stirred at room temperature for 1 hour. The solvent was distilled away under reduced pressure, water (200 mL) was added to the residue, and extracted with ethyl acetate (200 mL). The extract was washed with saturated saline (200 mL), dried over anhydrous

magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 10:1) to give the title compound 6.97 g (yield 85%) as a pale yellow powder.

NMR ($CDCl_3$) δ 1.51 (9H, s), 1.94-2.17 (2H, m), 2.48 (3H, s), 3.17-3.33 (4H, m), 3.57-3.76 (4H, m), 6.29 (1H, d, J = 7.0 Hz), 7.10 (1H, dd, J = 8.8, 7.0 Hz), 7.24-7.32 (2H, m).

66b) 5-(2,3,5,6-Tetrahydro-7H-1,4-diazepin-1-yl)-2-methylimidazo[1,2-a]pyridine dihydrochloride

5-[4-(tert-Butoxycarbonyl-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl]-2-methylimidazo[1,2-a]pyridine (6.97 g) obtained in Example 66a) was added to concentrated hydrochloric acid (17.3 mL), and srirred at room temperature for 20 minutes. To the reaction solution was added ethanol (70 mL), and concentrated under reduced pressure. To the residue was added ethanol-ether, and the formed precipitate was collected by filtration. The solid was washed with ethanol (10 mL) and diethyl ether (10 mL), and dried under reduced pressure to give the title compound 4.99 g (yield 78%) as a white powder.

NMR (D_2O) δ 2.27-2.38 (2H, m), 2.56 (3H, s), 3.48-3.57 (2H, m), 3.57-3.78 (4H, m), 3.78-3.81 (2H, m), 7.09 (1H, d, J = 7.8 Hz), 7.52 (1H, d, J = 9.0 Hz), 7.71 (1H, s), 7.85 (1H, dd, J = 8.8, 7.8 Hz).

66c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 1.19 g (yield 93%) was obtained as a a colorless powder from 5-(2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)-2-methylimidazo[1,2-a]pyridine dihydrochloride (0.90 g).

NMR ($CDCl_3$) δ 0.49-0.83 (1H, m), 2.01-2.20 (2H, m), 2.47 (3H, s), 2.90-3.00 (2H, m), 3.14-3.22 (3H, m), 3.35-3.39 (1H, m), 3.53-3.65 (2H, m), 3.70-3.81 (3H, m), 6.20-6.28 (1H, m), 7.07-7.13 (1H, m), 7.24-7.30 (2H, m), 7.56 (1H, dd, J = 9.0, 7.2 Hz), 7.90-7.96 (4H, m), 8.47-8.48 (1H, m).

66d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl]-2-methylimidazo[1,2-a]pyridine hydrochloride

According to a similar manner to Example 1d), the title compound 1.12 g (yield 86%) was obtained as a white powder from 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl]-2-methylimidazo[1,2-a]pyridine (1.21 g) obtained in Example 66c).

NMR (DMSO-d_6) δ 1.23-1.69 (1H, m), 1.83-2.11 (2H, m), 2.50 (3H, s), 2.61-2.93 (3H, m), 3.12-3.31 (4H, m), 3.33-3.47 (1H, m), 3.47-3.82 (3H, m), 6.91-7.01 (1H, m), 7.52 (1H, d,

J = 8.4 Hz), 7.67-7.88 (3H, m), 7.96-8.03 (1H, m), 8.16-8.29 (3H, m), 8.66 (1H, br), LC/MS 511 (M-HCl).

Example 67

7-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine

67a) 2-Amino-4-(4-tert-butoxycarbonyl-1-piperazinyl)pyridine

A solution of 2-amino-4-chloropyridine (6.00 g) and 1-Boc-piperazine (13.0 g) in ethanol (50 mL) was srirred at 120°C for 7 hours. The reaction mixture was diluted with chloroform and aqueous potassium carbonate solution, and the organic layer was separated. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title compound 10.8 g (yield 83%) as a a white powder

NMR ($CDCl_3$) δ1.48 (9H, s), 3.23-3.28 (4H, m), 3.52-3.57 (4H, m), 4.25 (2H, br), 5.85 (1H, d, J = 3.3 Hz), 6.18 (1H, dd, J = 3.9 and 9.3 Hz), 7.83 (1H, d, J = 9.2 Hz).

67b) 7-[4-(tert-Butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine

A solution of 2-amino-4-(4-tert-butoxycarbonyl-1-piperazinyl)pyridine (1.39 g) obtained in Example 67a), 40% aqueous chloroacetaldehyde solution (1.18 g) and sodium hydrogen carbonate (0.42 g) in ethanol (20 mL) was refluxed

for 3 hours. The reaction solution was concentrated under reduced pressure, diluted with aqueous potassium carbonate solution, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate) to give the title compound 1.26 g (yield 83%) as a brown powder. NMR ($CDCl_3$) δ1.49 (9H, s), 3.17 (4H, t, J = 5.2 Hz), 3.60 (4H, t, J = 5.2 Hz), 6.59 (1H, dd, J = 2.4 and 7.6 Hz), 6.81 (1H, d, J = 2.6 Hz), 7.38 (1H, t, J = 0.6 Hz), 7.47 (1H, d, J = 1.0 Hz), 7.94 (1H, d, J = 7.8 Hz).

67c) 7-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine

5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine (0.70 g) obtained in Example 67b) was dissolved in concentrated hydrochloric acid (3 mL), and stirred at room temperature for 5 minutes. The reaction solution was concentrated under reduced pressure, and to the residue obtained by azeotropic distillation with ethanol were added DBU (0.70 g) and triethylamine (0.70 g) and dissolved in DMF (5 mL). This solution was added to a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoic acid (0.69 g), HOBt (0.53 g) and WSC (0.67 g) in DMF (15 mL), and stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, and diluted with

aqueous potassium carbonate solution. The mixture was extracted with THF and ethyl acetate, the extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate) and silica gel column chromatography (eluent: chloroform/methanol 30:1 → 10:1), andrecrystallized from ethyl acetate to give the title compound 0.27 g (yield 24%) as a white powder.

NMR ($CDCl_3$) δ2.91-2.96 (2H, m), 3.13 (2H, t, J = 5.1 Hz), 3.21 (2H, t, J = 5.1 Hz), 3.56-3.61 (2H, m), 3.65 (2H, t, J = 5.1 Hz), 3.71 (2H, t, J = 5.1 Hz), 6.55 (1H, dd, J = 2.4 and 7.5 Hz), 6.80 (1H, d, J = 2.1 Hz), 7.38 (1H, t, J = 0.6 Hz), 7.48 (1H, d, J = 1.5 Hz), 7.57 (1H, dd, J = 1.8 and 8.7 Hz), 7.89-7.96 (5H, m), 8.48 (1H, d, J = 1.5 Hz).

Elemental analysis for $C_{24}H_{23}ClN_4O_3S \cdot 0.2H_2O$

Calcd (%): C, 59.24 ; H, 4.85 ; N, 11.51

Found (%): C, 59.00 ; H, 4.69 ; N, 11.32.

Example 68

7-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

68a) 7-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 67b), the title compound 0.18 g (yield 57%) was obtained as a pale

brown powder from bromoacetone (0.10 mL).

NMR ($CDCl_3$) δ1.49 (9H, s), 2.39 (3H, d, J = 0.6 Hz), 3.15 (4H, t, J = 5.2 Hz), 3.59 (4H, t, J = 5.2 Hz), 6.51 (1H, dd, J = 2.4 and 7.6 Hz), 6.72 (1H, d, J = 2.2 Hz), 7.12 (1H, s), 7.47 (1H, d, J = 1.0 Hz), 7.83 (1H, dd, J = 0.8 and 7.6 Hz).

68b) 7-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 67c), the title compound 0.20 g (yield 75%) was obtained as a brown powder from 7-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (0.17 g) obtained in Example 68a).

NMR ($CDCl_3$) δ2.39 (3H, d, J = 0.9 Hz), 2.90-2.96 (2H, m), 3.11 (2H, t, J = 5.1 Hz), 3.19 (2H, t, J = 5.1 Hz), 3.56-3.61 (2H, m), 3.64 (2H, t, J = 5.1 Hz), 3.71 (2H, t, J = 5.1 Hz), 6.49 (1H, dd, J = 2.4 and 7.8 Hz), 6.71 (1H, d, J = 1.8 Hz), 7.13 (1H, s), 7.58 (1H, dd, J = 1.8 and 8.7 Hz), 7.85 (1H, d, J = 7.5 Hz), 7.90-7.97 (4H, m), 8.49 (1H, s).

Elemental analysis for $C_{25}H_{25}ClN_4O_3S$

Calcd (%): C, 60.41 ; H, 5.07 ; N, 11.27

Found (%): C, 60.11 ; H, 4.97 ; N, 11.10.

Example 69

7-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine

69a) 7-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-

ethoxycarbonylimidazo[1,2-a]pyridine

A solution of 2-amino-4-(4-tert-butoxycarbonyl-1-piperazinyl)pyridine (1.67 g) obtained in Example 67a) and ethyl bromopyruvate (1.76 mL) in ethanol (30 mL) was refluxed for 5 hours. The reaction solution was concentrated under reduced pressure, diluted with aqueous potassium carbonate solution, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 20:1) to give the title compound 0.55 g (yield 24%) as a pale yellow powder. NMR ($CDCl_3$) δ1.42 (3H, t, J = 7.2 Hz), 1.49 (9H, s), 3.19 (4H, t, J = 5.0 Hz), 3.60 (4H, t, J = 5.0 Hz), 4.43 (2H, q, J = 7.2 Hz), 6.67 (1H, dd, J = 2.6 and 7.8 Hz), 6.79 (1H, d, J = 1.8 Hz), 7.92 (1H, d, J = 7.6 Hz), 7.98 (1H, s).

69b) 7-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine

7-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine (0.55 g) obtained in Example 69a) was dissolved in 1N sodium hydroxide solution (4 mL) and ethanol (15 mL), and stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure, and adjusted to pH 3 by adding 1N hydrochloric acid, followed by washing with ethyl acetate.

To the aqueous layer was added sodium chloride, and the deposited precipitate was collected by filtration. The solid obtained was added by portions at room temperature to a THF solution (5 mL) of 1M borane-THF complex, and stirred at room temperature for 1 hour. The reaction solution was poured into ice-water, and stirred for 10 minutes. The mixture was adjusted to pH 3 by adding concentrated hydrochloric acid, and stirred at 0°C for 1 hour. To the reaction solution was added aqueous potassium carbonate solution to make it alkaline, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue of brown oil was dissolved in concentrated hydrochloric acid (2 mL) and ethanol (2 mL), and stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and to the residue obtained by subjecting to azeotropic distillation with ethanol were added DBU (0.30 g) and triethylamine (0.30 g) and dissolved in DMF (5 mL). This solution was added to a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoic acid (0.32 g), HOBt (0.23 g) and WSC (0.29 g) in DMF (15 mL), and stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and diluted with aqueous potassium carbonate solution. The mixture was extracted with chloroform, the extract was dried over

anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 20:1), and crystallized from ethyl acetate-diethyl ether to give the title compound 0.15 g (yield 29%) as a white powder.

NMR ($CDCl_3$) δ2.50 (1H, br), 2.92 (2H, t, J = 7.6 Hz), 3.15 (2H, t, J = 5.1 Hz), 3.12 (2H, t, J = 5.1 Hz), 3.20 (2H, t, J = 5.1 Hz), 3.55-3.72 (6H, m), 4.78 (2H, s), 6.53 (1H, dd, J = 2.4 and 7.8 Hz), 6.71 (1H, d, J = 2.2 Hz), 7.34 (1H, s), 7.57 (1H, dd, J = 1.8 and 6.8 Hz), 7.88-7.97 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{25}H_{25}ClN_4O_4S \cdot H_2O \cdot 0.1EtOAc$

Calcd (%): C, 56.51; H, 5.19; N, 10.38

Found (%): C, 56.78; H, 5.20; N, 10.12.

Example 70

5-[4-[3-[(4-bromophenyl)sulfonyl]propionyl]-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 0.44 g (yield 64%) was obtained as a colorless powder by using 2-hydroxymethyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (0.50 g) obtained in Example 13c) and 3-[(4-bromophenyl)sulfonyl]propanoic acid (WO 09805635: 0.40 g).

NMR ($CDCl_3$) δ2.93 (2H, t, J = 7.7), 3.10-3.17 (4H, m), 3.51

(2H, t, J = 7.7), 3.75-3.84 (4H, m), 4.90 (2H, s), 6.40 (1H, d, J = 7.4), 7.33 (1H, d, J =7.4), 7.46 (1H, d, J =8.8), 7.58 (1H, s), 7.72-7.83 (4H, m). LC/MS 507(M).

Elemental analysis for $C_{21}H_{23}BrN_4O_4S$

Calcd (%): C, 48.00 ; H, 4.80 ; N, 10.66

Found (%): C, 47.86 ; H, 4.60 ; N, 10.46.

Example 71

6-(4-(3-((6-Chloro-2-naphthyl)sulfonyl)propionyl)-1-piperazinyl)imidazo[1,2-a]pyridine

71a) tert-Butyl 4-(6-nitro-3-pyridinyl)-1-piperazinecarboxylate

1-Boc-piperazine (2.79 g) and 5-bromo-2-nitropyridine (1.02 g) was dissolved in N-methylpyrrolidone (15 mL), and stirred at 120°C for 3 hours. The reaction mixture was diluted with water, and the precipitate was collected by filtration to give the title compound 1.27 g (yield 82%) as a white powder.

NMR ($CDCl_3$) δ1.49 (9H,s), 3.43-3.52 (4H, m), 3.62-3.67 (4H, m), 7.21 (1H, dd, J = 3.0, 9.0), 8.14 (1H, d, J = 3.0), 8.19 (1H, d, J =9.2).

71b) tert-Butyl 4-(6-amino-3-pyridinyl)-1-piperazinecarboxylate

tert-Butyl 4-(6-nitro-3-pyridinyl)-1-piperazinecarboxylate (308 mg) obtained in Example 71a) was dissolved in ethanol (20 mL), and 10% palladium carbon (80

mg) was added thereto, followed by catalytic reduction at room temperature and at atmospheric pressure for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give the title compound 280 mg (quantitative) as a brown oil.

NMR ($CDCl_3$) δ1.48 (9H, s), 2.95 (4H, t, J = 4.5), 3.55-3.58 (4H, m), 6.51 (1H, dd, J = 0.9, 9.0), 7.19 (1H, dd, J = 3.0, 8.7), 7.73 (1H, d, J =2.1).

71c) tert-Butyl 4-imidazo[1,2-a]pyridin-6-yl-1-piperazinecarboxylate

tert-Butyl 4-(6-amino-3-pyridinyl)-1-piperazinecarboxylate (240 mg) obtained in Example 71b) and 40% aqueous chloroacetaldehyde solution (338 mg) was dissolved in ethanol (20 mL), and refluxed for 15 hours. The reaction solution was concentrated under reduced pressure, and the residue was diluted with aqueous sodium hydrogen carbonate solution, followed by extracting with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure to give the title compound 280 mg (quantitative) as a brown oil.

NMR ($CDCl_3$) δ1.49 (9H,s), 3.00 (4H, t, J = 5.2), 3.58-3.68 (4H, m), 7.05 (1H, dd, J = 2.2, 9.8), 7.51-7.57 (4H, m).

71d) 6-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]imidazo[1,2-a]pyridine

tert-Butyl 4-imidazo[1,2-a]pyridin-6-yl-1-piperazinecarboxylate (260 mg) obtained in Example 71c) was dissolved in concentrated hydrochloric acid (2 mL) and ethanol (2 mL), and stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and subjected to azeotropic distillation with ethanol to remove water. To the residue obtained were added DBU (262 mg) and triethylamine (261 mg), and dissolved in acetonitrile (5 mL). This solution was added to a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoic acid (257 mg), HOBt (198 mg) and WSC (247 mg) in acetonitrile (25 mL), and stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, diluted with aqueous potassium carbonate solution, and extracted with THF and ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate) to give the title compound 130 mg (yield 31%) as a green powder.

NMR ($CDCl_3$) δ2.91-2.97 (4H, m), 3.06 (2H, t, J = 5.1), 3.56-3.61 (2H, m), 3.66 (2H, t, J = 5.1), 3.72 (2H, t, J = 5.1), 7.01 (1H, dd, J = 2.1, 9.9), 7.51-7.60 (5H, m), 7.89-7.97 (4H, m), 8.48 (1H, s).

Example 72

6-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

72a) 2-Methyl-6-(1-piperazinyl)imidazo[1,2-a]pyridine

tert-Butyl 4-(6-amino-3-pyridinyl)-1-piperazinecarboxylate (0.99 g) obtained in Example 71b) and bromoacetone (0.66 mL) was dissolved in ethanol (25 mL), and refluxed for 15 hours. The reaction solution was concentrated under reduced pressure, and the residue was diluted with aqueous potassium carbonate solution, followed by extracting with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 10/1) to give the title compound 0.30 g (yield 39%) as a green powder.

NMR ($CDCl_3$) δ2.42 (3H, d, J = 0.6), 2.99-3.09 (8H, m), 6.99 (1H, dd, J= 2.2. 9.2), 7.26 (1H, dd, J = 0.8, 6.2), 7.39 (1H, dd, J = 9.6, 0.6), 7.47 (1H, d, J =2.2).

72b) 6-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine

3-[(6-Chloro-2-naphthyl)sulfonyl]propanoic acid (414 mg) and HOBt (319 mg) was dissolved in acetonitrile (20 mL), and WSC (399 mg) was added theterto, followed by stirring at room temperature for 15 minutes. A solution of 2-methyl-6-(1-piperazinyl)imidazo[1,2-a]pyridine (300 mg)

obtained in Example 72a) and triethylamine (421 mg) in DMF (5 mL) was added theterto, and stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure, diluted with aqueous sodium hydrogen carbonate solution, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate) to give the title compound 570 mg (yield 83%) as a green powder.

NMR ($CDCl_3$) δ2.42 (3H, d, J = 0.6), 2.91-2.96 (4H, m), 3.03 (2H, t, J = 4.8), 3.56-3.61 (2H, m), 3.64 (1H, t, J = 5.1), 3.72 (2H, t, J = 5.1), 6.95 (1H, dd, J =2.1, 9.9), 7.41 (1H, d, J =9.0), 7.46 (1H, d, J =1.5), 7.58 (1H, dd, J =2.1, 9.0), 7.89-7.96 (4H, m), 8.48 (1H, s).

Example 73

7-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-3-(ethoxymethyl)imidazo[1,2-a]pyridine and [7-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]imidazo[1,2-a]pyridin-3-yl]methanol

tert-Butyl 4-(imidazo[1,2-a]pyridin-7-yl)-1-piperazinecarboxylate (278 mg) obtained in Example 67b) was dissolved in ethanol (5 mL), and formalin (0.2 mL) was added thereto, followed by refluxing for 1 hour. Formalin (0.2 mL) was added, and refluxed for 2 hours, and further

formalin (0.2 mL) was added thereto, followed by refluxing for 2 hours. The reaction solution was concentrated under reduced pressure, diluted with aqueous potassium carbonate solution, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue was dissolved in concentrated hydrochloric acid (2 mL), and stirred at room temperature for 15 minutes. The reaction solution was concentrated under reduced pressure, and subjected to azeotropic distillation with ethanol to remove water. To the residue obtained were added DBU (280 mg) and triethylamine (279 mg), and dissolved in DMF (5 mL). This solution was added to a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoic acid (275 mg), HOBt (211 mg) and WSC (275 mg) in acetonitrile (20 mL), and stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, diluted with aqueous potassium carbonate solution, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 20/1) to give 7-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-3-(ethoxymethyl)imidazo[1,2-a]pyridine 43 mg (yield 13%) as a

colorless powder and [7-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]imidazo[1,2-a]pyridin-3-yl]methanol 80 mg (yield 25%) as a colorless powder.

7-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-3-(ethoxymethyl)imidazo[1,2-a]pyridine

NMR ($CDCl_3$) δ1.19 (3H, t, J = 6.9), 2.93 (2H, d, J = 7.9), 3.15 (2H, t, J = 5.0), 3.23 (2H, t, J = 5.0), 3.48 (2H, q, J = 6.9), 3.55-3.72 (6H, m), 4.75 (2H, s), 6.61 (1H, dd, J = 2.4, 7.4), 6.79 (2H, d, J = 2.6), 7.42 (1H, s), 7.67 (1H, dd, J =1.8, 8.8), 7.93-7.97 (3H, m), 8.04 (1H, d, J =7.6), 8.49 (1H, s).

Elemental analysis for $C_{27}H_{29}ClN_4O_4S \cdot 0.3H_2O$

Calcd (%): C, 59.34 ; H, 5.46 ; N, 10.25

Found (%): C, 59.43 ; H, 5.27 ; N, 10.07

[7-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]imidazo[1,2-a]pyridin-3-yl]methanol

NMR ($CDCl_3$) δ2.93 (2H, d, J = 7.9), 3.17 (2H, t, J = 5.0), 3.23 (2H, t, J = 5.0), 3.55-3.68 (6H, m), 4.88 (2H, s), 6.63 (1H, dd, J = 2.4, 7.4), 6.75 (1H, d, J = 1.8), 7.33 (1H, s), 7.58 (1H, dd, J =1.8, 8.8), 7.89-7.98 (4H, m), 8.12 (1H, d, J =7.4), 8.49 (1H, s).

Elemental analysis for $C_{25}H_{25}ClN_4O_4S$

Calcd (%): C, 58.53 ; H, 4.91 ; N, 10.92

Found (%): C, 58.25 ; H, 4.95 ; N, 11.26

Example 74

Ethyl 7-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine-3-carboxylate

74a) Ethyl 7-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine-3-carboxylate

A solution of tert-butyl 4-(2-amino-4-pyridyl)-1-piperazinecarboxylate (1.20 g) obtained in Example 67a) and ethyl 2-chloroacetoacetate (3.0 mL) in ethanol (30 mL) was refluxed for 15 hours. The reaction solution was concentrated under reduced pressure, diluted with aqueous potassium carbonate solution, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate), and washed with diisopropyl ether-hexane to give the title compound 0.59 g (yield 35%) as a pale brown powder.

NMR ($CDCl_3$) δ1.42 (3H, t, J = 7.2), 1.49 (9H, s), 2.65 (3H, s), 3.28 (4H, t, J = 5.2), 3.61 (4H, t, J = 5.2), 4.39 (2H, q, J = 7.2), 6.68 (1H, dd, J = 2.6, 7.6), 6.77 (1H, d, J = 2.2), 9.06 (1H, d, J = 7.8).

74b) Ethyl 7-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine-3-carboxylate

Ethyl 7-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-

methylimidazo[1,2-a]pyridine-3-carboxylate (194 mg) obtained in Example 74a) was dissolved in concentrated hydrochloric acid (1 mL), and stirred at room temperature for 5 minutes. The reaction solution was concentrated under reduced pressure, and to the residue obtained by subjecting to azeotropic distillation with ethanol were added DBU (152 mg) and triethylamine (152 mg), followed by dissolving in acetonitrile (5 mL). This solution was added to a suspension of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoic acid (149 mg), HOBt (115 mg) and WSC (144 mg) in acetonitrile (15 mL), and stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, diluted with aqueous sodium hydrogen carbonate solution, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate → ethyl acetate/methanol 10/1), and crystallized from ethyl acetate to give the title compound 160 mg (yield 68%) as a colorless powder.

NMR ($CDCl_3$) δ1.43 (3H, t, J = 6.9), 2.65 (3H, s), 2.91-2.96 (2H, m), 3.24 (2H, t, J = 5.1), 3.33 (2H, t, J = 5.1), 3.56-3.62 (2H, m), 3.67 (2H, t, J = 5.1), 3.73 (2H, t, J = 5.1), 4.40 (2H, q, J = 6.9), 6.66 (1H, dd, J = 3.0, 7.2),

6.76 (1H, d, J = 4.2), 7.58 (1H, dd, J =1.8, 8.8), 7.90-7.97 (4H, m), 8.49 (1H, s), 9.08 (1H, d, J =7.5).

Elemental analysis for $C_{28}H_{29}ClN_4O_5S$

Calcd (%): C, 59.10 ; H, 5.14 ; N, 9.85

Found (%): C, 58.84 ; H, 5.06 ; N, 9.72

Example 75

7-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-3-(ethoxymethyl)-2-methylimidazo[1,2-a]pyridine

75a) tert-Butyl 4-[3-(hydroxymethyl)-2-methylimidazo[1,2-a]pyridin-7-yl]-1-piperazinecarboxylate

Ethyl 7-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine-3-carboxylate (194 mg) obtained in Example 74a) was dissolved in THF (20 mL), and Lithium borohydride (327 mg) was added by portions, followed by stirring at room temperature for 2 hours. Water was added and stirred for 10 minutes, and 1N hydrochloric acid was added to the mixture with cooling to 0°C to make it acidic, followed by stirring at room temperature for 1 hour. After making it alkaline by adding potassium carbonate, the mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure to give the title compound 190 mg (quantitative) as a colorless powder.

NMR ($CDCl_3$) δ1.49 (9H, s), 2.31 (3H, s), 3.17-3.21 (4H, m), 3.57-3.61 (4H, m), 3.70 (1H, br), 4.86 (2H, s), 6.58-6.62 (1H, m), 6.71 (1H, s), 8.01 (1H, d, J = 8.0).

75b) 7-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-3-(ethoxymethyl)-2-methylimidazo[1,2-a]pyridine

tert-Butyl 4-[3-(hydroxymethyl)-2-methylimidazo[1,2-a]pyridin-7-yl]-1-piperazinecarboxylate (290 mg) obtained in Example 75a) was dissolved in concentrated hydrochloric acid (1 mL), and stirred at room temperature for 5 minutes. The reaction solution was concentrated under reduced pressure, and the residue was subjected to azeotropic distillation with ethanol to remove water. To the residue obtained were added DBU (255 mg) and triethylamine (254 mg), and dissolved in acetonitrile (5 mL). This solution was added to a suspension of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoic acid (250 mg), HOBt (192 mg) and WSC (241 mg) in acetonitrile (15 mL), and stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, diluted with aqueous potassium carbonate solution, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent: ethyl acetate) to give the title

compound 190 mg (yield 41%) as a pale brown powder.

NMR ($CDCl_3$) δ1.19 (3H, t, J = 6.9), 2.40 (3H, s), 2.92 (2H, t, J = 7.2), 3.24 (2H, t, J = 7.2), 3.13 (2H, t, J = 5.1), 3.21 (2H, t, J = 5.1), 3.49 (2H, q, J = 6.9), 3.56-3.72 (6H, m), 4.71 (2H, s), 6.54 (1H, dd, J =2.7, 7.5), 6.70 (1H, d, J = 2.1), 7.57 (1H, dd, J = 1.8, 9.0), 7.89-7.96 (5H, m), 8.47 (1H, s).

Elemental analysis for $C_{28}H_{31}ClN_4O_4S \cdot 0.5H_2O$

Calcd (%): C, 59.62 ; H, 5.72 ; N, 9.93

Found (%): C, 59.69 ; H, 5.76 ; N, 9.67

Example 76

1-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-4-[2-(1-hydroxy-1-methylethyl)imidazo[1,2-a]pyridin-5-yl]-2-piperazinecarboxamide

76a) Ethyl 5-[3-carbamoyl-4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine-2-carboxylate

5-[3-(Carbamoyl)-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine (4.00 g) obtained in Example 60a) was dissolved in ethanol (150 mL), and di-tert-butyl carbonate (2.75 g) was added dropwise at room temperature thereto, and the reaction solution was stirred at room temperature for 24 hours. The reaction solution was concentrated under reduced pressure, and water and ethyl acetate were added to the residue, followed by collecting the precipitate to give the title compound 4.50

g (yield 86%) as a colorless powder.

NMR ($CDCl_3$) δ1.46 (3H, t, J = 6.9), 1.54 (9H, s), 2.60-2.66 (1H, m), 2.94-3.02 (1H, m), 3.15-3.38 (2H, m), 4.26-4.30 (2H, m), 4.41-4.54 (2H, m), 4.82-4.98 (1H, m), 6.31 (1H, d, J = 7.5), 6.51-6.98 (1.5H, m), 7.20 (1H, dd, J =9.0, 7.5), 7.44 (1H, d, J = 8.4), 7.75 (0.5H, br), 8.82-9.02 (1H, m).

76b) tert-Butyl 2-carbamoyl-4-[2-(1-hydroxy-1-methylethyl)imidazo[1,2-a]pyridin-5-yl]piperazine-1-carboxylate and tert-butyl 4-(2-acetylimidazo[1,2-a]pyridin-5-yl)-2-(carbamoyl)piperazine-1-carboxylate

Ethyl 5-[3-carbamoyl-4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine-2-carboxylate 2.00 g) was dissolved in THF (200 mL), and 1M solution of methylmagnesium bromide in THF (48 mL) was added dropwise thereto. After stirring the reaction mixture at room temperature for 3 hours, saturated aqueous ammmonium chloride solution (100 mL) was added dropwise. The reaction mixture was stirred at room temperature for 10 minutes, and filtered to remove the insoluble materials. To the filtrate was added ethyl acetate, the organic layer was separated, dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol 20/1 → 15/1) to give tert-butyl 2-carbamoyl-4-[2-(1-hydroxy-1-

methylethyl)imidazo[1,2-a]pyridin-5-yl]piperazine-1-carboxylate 0.65 g (yield 34%) as a yellow powder and tert-butyl 4-(2-acetylimidazo[1,2-a]pyridin-5-yl)-2-(carbamoyl)piperazine-1-carboxylate 0.68 g (yield 37%) as a yellow solid.

tert-Butyl 2-carbamoyl-4-[2-(1-hydroxy-1-methylethyl)imidazo[1,2-a]pyridin-5-yl]piperazine-1-carboxylate

NMR ($CDCl_3$) δ1.53 (9H, s), 1.71 (3H, s), 1.80-4.35 (8H, m), 4.82-4.95 (1H, m), 6.23-6.33 (2H, m), 7.11-7.21 (1H, m), 7.36-7.45 (1H, m), 8.12-8.35 (1H, m).

tert-Butyl 4-(2-acetylimidazo[1,2-a]pyridin-5-yl)-2-(carbamoyl)piperazine-1-carboxylate

NMR ($CDCl_3$) δ1.54 (9H, s), 1.70-4.40 (10H, m), 4.82-4.95 (1H, m), 6.30-6.46 (2H, m), 7.20-7.53 (2H, m), 8.70-9.00 (1H, m).

76c) 1-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-4-[2-(1-hydroxy-1-methylethyl)imidazo[1,2-a]pyridin-5-yl]-2-piperazinecarboxamide

According to a similar manner to Example 37d), the title compound 0.11 g (yield 12%) was obtained as a colorless powder from tert-butyl 2-carbamoyl-4-[2-(1-hydroxy-1-methylethyl)imidazo[1,2-a]pyridin-5-yl]piperazine-1-carboxylate (0.64 g) obtained in Example 76b).

NMR ($CDCl_3$) δ1.72 (6H, s), 1.80-4.43 (12H, m), 5.41-6.89 (3H, m), 7.14-7.21 (1H, m), 7.38 (1H, d, J = 9.3), 7.62 (1H, dd, J = 2.1, 9.0), 7.91-8.13 (4H, m), 8.32 (1H, s), 8.50 (1H, s).

Example 77

1-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-4-[2-(1-hydroxyethyl)imidazo[1,2-a]pyridin-5-yl]-2-piperazinecarboxamide

77a) tert-Butyl 2-carbamoyl-4-[2-(1-hydroxyethyl)imidazo[1,2-a]pyridin-5-yl]piperazine-1-carboxylate

tert-Butyl 4-(2-acetylimidazo[1,2-a]pyridin-5-yl)-2-(carbamoyl)piperazine-1-carboxylate (0.65 g) obtained in Example 76b) was dissolved in methanol (10 mL) and THF (5 mL), sodium borohydride (80 mg) was added , and stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, the residue was diluted with aqueous potassium carbonate solution, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure to give the title compound 0.55 g (yield 84%) as a yellow solid.

NMR ($CDCl_3$) δ1.53 (9H, s), 1.65-1.69 (3H, d, J = 6.6), 2.54-2.62 (1H, m), 2.90-3.02 (1H, m), 3.19-3.48 (3H, m), 4.25-4.31 (2H, m), 4.87 (1H, br), 5.10 (1H, q, J = 6.6),

6.24 (1H, d, J = 6.8), 6.43 (1H, br), 7.13 (1H, dd, J = 8.8, 7.2), 7.34 (1H, d, J = 9.2), 8.20 (1H, br).

77b) 1-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-4-[2-(1-hydroxyethyl)imidazo[1,2-a]pyridin-5-yl]-2-piperazinecarboxamide

According to a similar manner to Example 37d), the title compound 0.11 g (yield 14%) was obtained as a colorless powder from tert-butyl 2-(carbamoyl)-4-[2-(1-hydroxyethyl)imidazo[1,2-a]pyridin-5-yl]piperazine-1-carboxylate (0.54 g) obtained in Example 77a).

NMR ($CDCl_3$) δ1.69 (3H, d, J = 6.6), 2.55-5.16 (12H, m), 5.43 (1H, m), 5.78 (1H, br), 6.26 (1H, d, J = 7.2), 6.82 (1H, br), 7.16 (1H, dd, J = 7.5, 8.7), 7.38 (1H, d, J = 9.0), 7.62 (1H, dd, J = 8.7, 2.0), 7.91-8.15 (4H, m), 8.36 (1H, s), 8.50 (1H, s).

Elemental analysis for $C_{27}H_{28}ClN_5O_5S \cdot 0.5H_2O$

Calcd (%): C, 55.14 ; H, 5.14 ; N, 11.91

Found (%): C, 55.21 ; H, 5.47 ; N, 11.81

Example 78

1-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-4-[2-(2-hydroxyethyl)imidazo[1,2-a]pyridin-5-yl]-2-piperazinecarboxamide

78a) tert-Butyl 2-(carbamoyl)-4-[2-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-5-yl]piperazine-1-carboxylate

According to a similar manner to Example 44b), the title compound 2.20 g (yield 37%) was obtained as a yellow powder from ethyl 5-fluoroimidazo[1,2-a]pyridine-2-acetate (3.1 g) obtained in Example 44a) and 2-piperazinecarboxamide (5.41 g).

NMR ($CDCl_3$) δ 1.22-1.32 (3H, m), 1.53 (9H, s), 2.58-2.66 (1H, m), 2.90-3.01 (1H, m), 3.22-3.40 (2H, m), 3.89 (2H, s), 4.14-4.30 (4H, m), 4.87 (1H, br), 5.79-5.86 (1H, br), 6.19 (1H, br), 6.25 (1H, dd, J = 1.5, 7.2), 7.13 (1H, dd, J = 8.8, 7.0), 7.35 (1H, d, J = 8.8), 8.26 (1H, br).

78b) tert-Butyl 2-(carbamoyl)-4-[2-(2-hydroxyethyl)imidazo[1,2-a]pyridin-5-yl]piperazine-1-carboxylate

According to a similar manner to Example 73a), the title compound 0.67 g (quantitative) was obtained as a colorless powder from tert-butyl 2-(carbamoyl)-4-[2-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-5-yl]piperazine-1-carboxylate (0.72 g) obtained in Example 78a).

NMR ($CDCl_3$) δ 1.53 (9H, s), 2.54-2.62 (1H, m), 2.91-3.08 (3H, m), 3.21-3.30 (2H, m), 3.71-3.78 (1H, m), 4.02 (2H, t, J = 5.8), 4.26-4.32 (2H, m), 4.87 (1H, br), 6.04-6.35 (3H, m), 7.13 (1H, dd, J = 8.8, 7.2), 7.31 (1H, d, J = 8.8), 8.17 (1H, br m).

78c) 1-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-4-[2-(2-hydroxyethyl)imidazo[1,2-a]pyridin-5-yl]-2-

piperazinecarboxamide

According to a similar manner to Example 37d), the title compound 0.16 g (yield 17%) was obtained as a colorless powder from tert-butyl 2-(carbamoyl)-4-[2-(2-hydroxyethyl)imidazo[1,2-a]pyridin-5-yl]piperazine-1-carboxylate (0.64 g) obtained in Example 78b).

NMR ($CDCl_3$) δ2.56 (1H, dd, J = 4.5, 12.0), 2.64-4.21 (13H, m), 4.41 (1H, d, J = 12.0), 5.42 (1H, m), 5.68 (1H, br), 6.25 (1H, d, J = 6.3), 6.84 (1H, br), 7.14 (1H, dd, J = 7.5, 8.7), 7.34 (1H, d, J = 8.7), 7.61 (1H, dd, J = 8.7, 2.1), 7.90-8.00 (4H, m), 8.22 (1H, s), 8.48 (1H, s).

Elemental analysis for $C_{27}H_{28}ClN_5O_5S \cdot 0.5H_2O$

Calcd (%): C, 56.00 ; H, 5.05 ; N, 12.09

Found (%): C, 55.92 ; H, 5.35 ; N, 12.01

Example 79

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-2-[(methylthio)methyl]imidazo[1,2-a]pyridine

By sequentially conducting similar reaction to Example 55a) and Example 55b), the title compound 0.63 g (yield 24%) was obtained as a pale yellow amorphous powder from 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine (1.70 g) obtained in Example 13b).

NMR (300, $CDCl_3$) δ 2.18 (3H, s), 2.96 (2H, t, J = 7.8), 3.04-3.12 (4H, m), 3.61 (1H, t, J = 8.1), 3.74-3.83 (4H, m),

3.88 (2H, s), 6.26 (1H, d, J = 7.2), 7.18 (1H, dd, J = 7.2, 9.0), 7.37 (1H, d, J = 8.7), 7.47 (1H, s), 7.61 (1H, dd, J = 9.0, 2.1), 7.95-7.98 (4H, m), 8.50 (1H, s).

Elemental analysis for $C_{26}H_{27}ClN_4O_3S_2 \cdot 0.5H_2O \cdot 0.2AcOEt$

Calcd (%): C, 56.50; H, 5.24; N, 9.83

Found (%): C, 56.72; H, 5.38; N, 9.58

Example 80

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-2-[(methylsulfinyl)methyl]imidazo[1,2-a]pyridine

According to a similar manner to Example 56, the title compound 200 mg (yield 36%) was obtained as a colorless powder from 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-2-[(methylthio)methyl]imidazo[1,2-a]pyridine (540 mg) obtained in Example 79.

NMR ($CDCl_3$) δ 2.62 (3H, s), 2.94 (2H, t, J = 7.8), 3.04-3.12 (4H, m), 3.60 (1H, dd, J = 6.3, 7.8), 3.72-4.25 (6H, m), 6.29 (1H, dd, J = 0.9, 7.2), 7.21 (1H, dd, J = 7.2, 9.0), 7.37 (1H, d, J = 8.7), 7.58-7.63 (2H, m), 7.90-7.97 (4H, m), 8.48 (1H, d, J = 1.2).

Elemental analysis for $C_{26}H_{27}ClN_4O_4S_2 \cdot H_2O \cdot 0.5AcOEt$

Calcd (%): C, 54.14; H, 5.35; N, 9.02

Found (%): C, 54.23; H, 5.35; N, 8.84

Example 81

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-2-[(methylsulfonyl)methyl]imidazo[1,2-a]pyridine

According to a similar manner to Example 57, the title compound 310 mg (yield 54%) was obtained as a colorless powder from 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl]-1-piperazinyl]-2-[(methylthio)methyl]imidazo[1,2-a]pyridine (540 mg) obtained in Example 79.

NMR ($CDCl_3$) δ 2.95 (2H, t, J = 7.5), 3.00 (3H, s), 3.04-3.12 (4H, m), 3.60 (1H, t, J = 7.8), 3.73-3.80 (4H, m), 4.46 (2H, s), 6.32 (1H, dd, J = 0.9, 7.2), 7.24 (1H, dd, J = 7.2, 9.0), , 7.37 (1H, d, J = 9.0), 7.60 (1H, dd, J = 1.8, 8.7), 7.69 (1H, s), 7.90-7.97 (4H, m), 8.48-8.56 (1H, m).

Elemental analysis for $C_{26}H_{27}ClN_4O_5S_2$

Calcd (%): C, 54.30 ; H, 4.73 ; N, 9.74

Found (%): C, 54.23 ; H, 4.44 ; N, 9.48

Example 82

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-methoxymethyl-2-methylimidazo[1,2-a]pyridine

82a) 3-Methoxymethyl-2-methyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine (3.47 g) obtained in Example 84a) was added to concentrated

hydrochloric acid (8.2 mL), and stirred at room temperature for 20 minutes. To the reaction solution was added ethanol (50 mL), and the mixture was concentrated under reduced pressure. The residue was diluted with methanol-diethyl ether, and the formed precipitate was collected by filtration. The solid was washed with diethyl ether (10 mL), and dried under reduced pressure to give the title compound 2.50 g (yield 75%) as a white crystal.

NMR (D_2O) δ 2.59 (3H, d, J = 2.6), 3.19-3.44 (2H, m), 3.44-3.74 (6H, m), 3.46 (3H, s), 5.07-5.17 (2H, m), 7.37 (1H, d, J = 7.6), 7.70 (1H, d, J = 8.8), 7.93 (1H, dd, J = 8.8, 7.6).

82b) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-methoxymethyl-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 390 mg (yield 64%) was obtained from 3-methoxymethyl-2-methyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (450 mg) obtained in Example 82a).

NMR ($CDCl_3$) δ 2.49 (3H, s), 2.69-2.84 (2H, m), 2.84-3.13 (3H, m), 3.18-3.41 (2H, m), 3.32 (3H, s), 3.41-3.68 (3H, m), 3.78-3.95 (1H, m), 3.39-4.64 (1H, m), 4.87 (1H, d, J = 12.4), 5.06 (1H, d, J = 12.4), 6.41 (1H, dd, J = 7.0, 1.2), 7.13 (1H, dd, J = 8.8, 7.0), 7.38 (1H, dd, J = 8.8, 1.2), 7.58-7.63 (1H, m), 7.92-7.98 (4H, m), 8.50 (1H, s).

Example 83

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-hydroxymethylimidazo[1,2-a]pyridine

83a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-3-hydroxymethylimidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]imidazo[1,2-a]pyridine (5.00 g) obtained in Example 1a) in ethanol (20 mL) was added 37% aqueous formaldehyde solution (50.5 mL) at room temperature, and warmed at 85°C for 16 hours. The solvent was distilled away under reduced pressure, and to the residue was added water (20 mL), followed by adjusting to pH 11 with 8N aqueous sodium hydroxide solution, and then extracted with chloroform (60 mL). The extract was washed with saturated saline (40 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 10/1) to give the title compound 3.28 g (yield 60%) as a white solid.

NMR ($CDCl_3$) δ 1.50 (9H, s), 2.85-2.97 (2H, m), 3.12-3.38 (4H, m), 3.68 (1H, br), 4.12-4.34 (2H, m), 4.87 (2H, s), 6.57 (1H, dd, J = 7.2, 1.2), 7.20 (1H, dd, J = 8.8, 1.2), 7.50 (1H, d, J = 8.8), 7.56 (1H, s).

83b) 3-Hydroxymethyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride

5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-3-hydroxymethylimidazo[1,2-a]pyridine (2.30 g) obtained in Example 83a) was added to concentrated hydrochloric acid (5.7 mL), and stirred at room temperature for 20 minutes. To the reaction solution were added ethanol (50 mL) and 2-propanol (50 mL), and the deposited crystals were collected by filtration. The crystals were washed with 2-propanol (10 mL) and diethyl ether (10 mL), and dried under reduced pressure to give the title compound 1.69 g (yield 80%) as a white crystal.

NMR (D_2O) δ 3.24-3.47 (2H, m), 3.47-3.74 (6H, m), 5.23 (2H, s), 7.34-7.40 (1H, m), 7.74-7.80(1H, m), 7.88-7.97 (2H, m).

83c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-hydroxymethylimidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 923 mg (yield 72%) was obtained from 3-hydroxymethyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine dihydrochloride (916 g) obtained in Example 83b).

NMR ($CDCl_3$) δ 2.76-3.13 (5H, m), 3.22-3.46 (2H, m), 3.46-3.70 (3H, m), 3.92-4.06 (1H, m), 4.57-4.73 (1H, m), 4.91 (2H, s), 6.52 (1H, d, J = 7.2), 7.19 (1H, dd, J = 8.8, 7.2), 7.51 (1H, dd, J = 8.8, 1.2), 7.56 (1H, s), 7.58-7.63 (1H, m), 7.89-7.99 (4H, m), 8.49 (1H, s).

83d) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-hydroxymethylimidazo[1,2-a]pyridine

hydrochloride

According to a similar manner to Example 1d), the title compound 870 mg (yield 81%) was obtained as a white powder from 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-hydroxymethylimidazo[1,2-a]pyridine (1.00 g) obtained in Example 83c)

NMR (DMSO-d_6) δ 2.56-3.01 (5H, m), 3.12-3.33 (2H, m), 3.33-3.84 (3H, m), 3.84-4.02 (1H, m), 4.17-4.36 (1H, m), 5.01 (2H, d, J = 6.2), 7.21-7.28 (1H, m), 7.72-7.86 (2H, m), 7.86-8.11 (2H, m), 8.11-8.37 (4H, m), 8.68 (1H, s).

Example 84

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine

84a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-methylimidazo[1,2-a]pyridine (6.33 g) obtained in Example 2a) in ethanol (20 mL) was added 37% aqueous formaldehyde solution (100 mL) at room temperature, and warmed at 85°C for 16 hours. The solvent was distilled away under reduced pressure, and to the residue was added water (20 mL), followed by adjusting to pH 11 with 8N aqueous sodium hydroxide solution, and then extracted with chloroform (60 mL). The extract was washed with saturated

saline (40 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 10/1) to give the title compound 5.96 g (yield 86%) as a pale yellow powder.

NMR ($CDCl_3$) δ 1.50 (9H, s), 2.47 (3H, s), 2.82-2.95 (2H, m), 3.11-3.37 (4H, m), 3.64 (1H, t, J = 5.2), 4.07-4.33 (2H, m), 4.86 (2H, d, J = 6.0), 6.52 (1H, dd, J = 7.0, 1.2), 7.15 (1H, dd, J = 8.8, 7.0), 7.40 (1H, dd, J = 8.8, 1.2).

84b) 3-Hydroxymethyl-2-methyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine

5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine (3.47 g) obtained in Example 84a) was added to concentrated hydrochloric acid (8.2 mL), and stirred at room temperature for 20 minutes. The solvent was distilled away under reduced pressure, and to the residue were added water (10 mL), 8N aqueous sodium hydroxide solution (20 mL) and sodium chloride (10 g), and then extracted with chloroform (50 mL). The extract was dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure to give the title compound 2.02 g (yield 82%) as a white solid.

NMR ($CDCl_3$) δ 2.48 (3H, s), 2.88-3.06 (2H, m), 3.06-3.34 (6H, m), 4.84 (2H, s), 6.55 (1H, dd, J = 7.0, 1.2), 7.16

(1H, dd, J = 8.8, 7.0), 7.39 (1H, dd, J = 8.8, 1.2).

84c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 700 mg (yield 68%) was obtained from 3-hydroxymethyl-2-methyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine (577 mg) obtained in Example 84b)

NMR ($CDCl_3$) δ 2.46 (3H, s), 2.68-3.13 (5H, m), 3.22-3.44 (2H, m), 3.48-3.72 (3H, m), 3.88-4.04 (1H, m), 4.57-4.72 (1H, m), 4.90 (2H, m), 6.47 (1H, d, J = 7.0, 1.2), 7.15 (1H, dd, J = 8.8, 7.0), 7.41 (1H, dd, J = 8.8, 1.2), 7.58-7.63 (1H, m), 7.89-7.95 (4H, m), 8.49 (1H, s).

Example 85

5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-hydroxyethyl-3-hydroxymethylimidazo[1,2-a]pyridine

85a) 5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(2-hydroxyethyl)-3-hydroxymethylimidazo[1,2-a]pyridine

To a solution of 5-[4-(tert-butoxycarbonyl)-1-piperazinyl]-2-(2-hydroxyethyl)imidazo[1,2-a]pyridine (3.46 g) obtained in Example 45b) in ethanol (15 mL) was added 37% aqueous formaldehyde solution (50.5 mL) at room temperature, and warmed at 85°C for 16 hours. The solvent was distilled away under reduced pressure, and to the residue was added water (15 mL), followed by adjusting to

pH 11 with 8N aqueous sodium hydroxide solution, and then extracted with chloroform (60 mL). The extract was washed with saturated saline (40 mL), dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 5/1) to give the title compound 2.37 g (yield 63%) as a white solid.

NMR ($CDCl_3$) δ 1.50 (9H, s), 1.95 (1H, br), 2.76-2.93 (2H, m), 3.01 (2H, t, J = 5.2), 3.12-3.41 (4H, m), 3.83 (1H, br), 3.97 (2H, t, J = 5.4), 4.09-4.31 (2H, m), 4.97 (2H, s), 6.51 (1H, dd, J = 7.0, 1.2), 7.16 (1H, dd, J = 8.8, 7.0), 7.37 (1H, dd, J = 8.8, 1.2).

85b) 2-(2-Hydroxyethyl)-3-hydroxymethyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine

5-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-(2-hydroxyethyl)-2-hydroxymethylimidazo[1,2-a]pyridine (1.88 g) obtained in Example 85a) was added to concentrated hydrochloric acid (4.1 mL, 50.0 mmol), and stirred at room temperature for 20 minutes. The solvent was distilled away under reduced pressure, and to the residue was added water (20 mL), followed by adjusting to pH 11 with 8N aqueous sodium hydroxide solution, and then extracted with chloroform (60 mL). The extract was washed with saturated saline (40 mL), dried over anhydrous magnesium sulfate, and

the solvent was distilled away under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol 5/1) to give the title compound 773 mg (yield 56%) as a pale yellow powder.

NMR (DMSO-d_6) δ 2.56-2.79 (2H, m), 2.79-3.03 (4H, m), 3.03-3.82 (4H, m), 3.62-3.82 (2H, m), 4.51 (1H, t, J = 6.6), 4.82 (1H, br), 4.97 (2H, d, J = 5.6), 6.56-6.63 (1H, m), 7.15-7.30 (2H, m).

85c) 5-[4-[3-[(6-Chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-(2-hydroxyethyl)-3-hydroxymethylimidazo[1,2-a]pyridine

According to a similar manner to Example 1c), the title compound 310 mg (yield 61%) was obtained from 2-(2-hydroxyethyl)-3-hydroxymethyl-5-(1-piperazinyl)imidazo[1,2-a]pyridine (303 mg) obtained in Example 85b)

NMR ($CDCl_3$) δ 2.64-2.88 (2H, m), 2.88-3.11 (5H, m), 3.25-3.40 (1H, m), 3.40-3.68 (4H, m), 3.83-4.03 (3H, m), 4.53-4.68 (1H, m), 4.95 (1H, d, J = 13.6), 5.11 (1H, d, J = 13.6), 6.43 (1H, dd, J = 7.0, 1.2), 7.14 (1H, dd, J = 8.8, 7.0), 7.35 (1H, dd, J = 8.8, 1.2), 7.57-7.62 (1H, m), 7.93-7.98 (4H, m), 8.48 (1H, s).

Formulation Example 1

An FXa inhibitor (e.g., a pharmaceutical composition

for treating deep vein thrombosis, cardiogenic cerebral infarction and the like) containing, as an active ingredient, the compound represented by the formula (I) or a salt thereof in the present invention can be produced, for example, by the following formulations.

Further, in the following formulations, the ingredients (additives) other than active ingredient may be those described in Japanese Pharmacopoeia, Pharmaceutical Specification out of Japanese Pharmacopoeia, or Pharmaceutical Additive Specification, and the like.

1. Capsules

(1) Compound obtained in Example 6	40 mg
(2) Lactose	70 mg
(3) Microcrystalline cellulose	9 mg
(4) Magnesium stearate	1 mg
One capsule	120 mg

(1), (2), (3) and a half of (4) are mixed and then granulated. The remainder of (4) is added to the granules and the whole is encapsulated in a gelatin capsule.

2. Capsules

(1) Compound obtained in Example 13	40 mg
(2) Lactose	70 mg
(3) Microcrystalline cellulose	9 mg
(4) Magnesium stearate	1 mg
One capsule	120 mg

(1), (2), (3) and a half of (4) are mixed and then granulated. The remainder of (4) is added to the granules and the whole is encapsulated in a gelatin capsule.

3. Capsules

(1)	Compound obtained in Example 14	40 mg
(2)	Lactose	70 mg
(3)	Microcrystalline cellulose	9 mg
(4)	Magnesium stearate	1 mg
	One capsule	120 mg

(1), (2), (3) and a half of (4) are mixed and then granulated. The remainder of (4) is added to the granules and the whole is encapsulated in a gelatin capsule.

4. Tablets

(1)	Compound obtained in Example 6	40 mg
(2)	Lactose	58 mg
(3)	Cornstarch	18 mg
(4)	Microcrystalline cellulose	3.5 mg
(5)	Magnesium stearate	0.5 mg
	One tablet	120 mg

(1), (2), (3), 2/3 of (4) and a half of (5) are mixed and then granulated. The remainders of (4) and (5) are added to the granules, followed by compressing into a tablet.

5. Tablets

(1)	Compound obtained in Example 13	40 mg

(2) Lactose 58 mg

(3) Cornstarch 18 mg

(4) Microcrystalline cellulose 3.5 mg

(5) Magnesium stearate 0.5 mg

One tablet 120 mg

(1), (2), (3), 2/3 of (4) and a half of (5) are mixed and then granulated. The remainders of (4) and (5) are added to the granules, followed by compressing into a tablet.

6. Tablets

(1) Compound obtained in Example 14 40 mg

(2) Lactose 58 mg

(3) Cornstarch 18 mg

(4) Microcrystalline cellulose 3.5 mg

(5) Magnesium stearate 0.5 mg

One tablet 120 mg

(1), (2), (3), 2/3 of (4) and a half of (5) are mixed and then granulated. The remainders of (4) and (5) are added to the granules, followed by compressing into a tablet.

Formulation Example 2

1. Injection

After 50 mg of the compound obtained in Example 6 is dissolved in 50 ml of Japanese Pharmacopoeia distilled

water for injection, Japanese Pharmacopoeia distilled water for injection is further added such that the whole volume is 100 mL. This solution is filtered under sterilizing condition. One milliliter aliquot of this solution is filled into a vial for injection, lyophilized, and sealed.

2. Injection

After 50 mg of the compound obtained in Example 13 is dissolved in 50 ml of Japanese Pharmacopoeia distilled water for injection, Japanese Pharmacopoeia distilled water for injection is further added such that the whole volume is 100 mL. This solution is filtered under sterilizing condition. One milliliter aliquot of this solution is filled into a vial for injection, lyophilized, and sealed.

3. Injection

After 50 mg of the compound obtained in Example 14 is dissolved in 50 ml of Japanese Pharmacopoeia distilled water for injection, Japanese Pharmacopoeia distilled water for injection is further added such that the whole volume is 100 mL. This solution is filtered under sterilizing condition. One milliliter aliquot of this solution is filled into a vial for injection, lyophilized, and sealed.

Experimental Example 1

Inhibitory action of human activated blood coagulation factor X (FXa)

Test method: A solution (225 μL) of 0.05M tris-hydrochloric acid buffers (pH = 8.3) containing 0.145 M of sodium chloride and 2 mM of calcium chloride, sample (5 μL; test compound dissolved in dimethyl sulfoxide) and human FXa (10 μL, 0.3 unit/ml) were added to a 96-well microplate and reacted at 37°C for about 10 minutes, and then a substrate (10 μL, 3 mM, S-2765) was added to be reacted at 37°C for 10 minutes. Then, after aqueous 50% acetic acid (25 μL) was added there to stop the reaction, the change of absorbance at 405 nm was measured by a microplate reader, and a concentration inhibiting FXa activity by 50% (IC_{50}) was calculated.

Experimental Results

IC_{50} is shown in Table 1. From this, it is clear that the compound of the present invention has an excellent FXa inhibiting effect.

Table 1

Example No.	IC_{50} (nM)	Example No.	IC_{50} (nM)
6	8	32	12
13	9	36	15
14	8	38	8
21	14	42	12
26	10	60	8

Experimental Example 2

Acute toxicity test in rat

Toxicity in single oral administration of the compound

of Example 13 (1000 mg/kg) to rats (male and female each 2) was examined.

Experimental Results

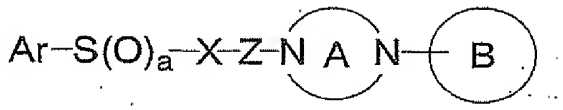
Since there was no example of death in each group, the approximate lethal dosage of the compound of Example 13 was concluded to be 1000 mg/kg or more.

Industrial Applicability

The compound (I) or its salt of the present invention has an excellent FXa inhibitory activity and few side effects of bleeding, is useful as an anticoagulant which can be orally absorbed, and is advantageously used for preventing and treating of various disorders based on thromboses.

CLAIMS

1. A compound represented by the formula (I):



(I)

wherein Ar represents an optionally substituted naphthyl group, an optionally substituted phenyl group, an optionally substituted indolyl group, or an optionally substituted benzothienyl group; X represents an optionally substituted divalent hydrocarbon group; Z represents -CO-, -SO-, or $-SO_2-$; ring A represents an optionally substituted

piperazine ring or an optionally substituted homopiperazine ring; ring B represents an optionally substituted imidazopyridine ring; and a represents 0, 1 or 2; or a salt theereof.

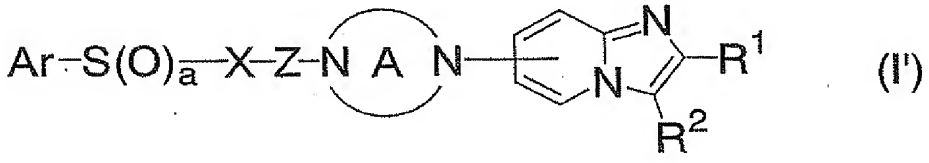
2. A prodrug of the compound according to claim 1.

3. The compound according to claim 1, wherein ring B is an optionally substituted imidazo[1,2-a]pyridine ring.

4. The compound according to claim 1, wherein ring B is an imidazo[1,2-a]pyridine ring which may be substituted with one or more substituents selected from a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted amino group, a nitro group and an optionally esterified or amidated carboxyl group.

5. The compound according to claim 1, wherein ring B is an imidazo[1,2-a]pyridine ring which may be substituted with an optionally substituted C_{1-4} alkyl group.

6. The compound according to claim 1, wherein the formula (I) is the formula (I')



(I')

wherein R^1 and R^2 each independently represent a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon atom, an optionally substituted amino group, a nitro group,

or an optionally esterified or amidated carboxyl group; and other symbols have the same meanings as defined in claim 1.

7. The compound according to claim 6, wherein R^1 and R^2 are each independently a hydrogen atom, or an optionally substituted C_{1-4} alkyl group.

8. The compound according to claim 1, wherein X is an optionally substituted divalent chain hydrocarbon group.

9. The compound according to claim 1, wherein X is an optionally substituted C_{1-8} alkylene group.

10. The compound according to claim 1, wherein Z is -CO-.

11. The compound according to claim 1, wherein ring A is an optionally substituted piperazine ring.

12. The compound according to claim 1, wherein a is 2.

13. The compound according to claim 6, wherein Ar is a naphthyl group substituted with a halogen atom, or a indolyl group substituted with a halogen atom; X is a C_{1-8} alkylene group; Z is -CO-; R^1 and R^2 are each independently a hydrogen atom, a C_{1-4} alkyl group which may be substituted with a hydroxyl group, or an esterified carboxyl group; and a is 2.

14. A compound selected from the group consisting of 5-[4-[3-[(5-chloro-2-indolyl)sulfonyl]propionyl]-1-piperazinyl-2-methylimidazo[1,2-a]pyridine, 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-1-piperazinyl]-2-hydroxymethylimidazo[1,2-a]pyridine, 5-[4-[3-[(6-chloro-2-

naphthyl)sulfonyl]propionyl]-3-(methylaminocarbonyl)methyl-1-piperazinyl]2-methylimidazo[1,2-a]pyridine, 5-[4-[3-[(6-chloro-2-naphthyl)sulfonyl]propionyl]-3-aminocarbonyl-1-piperazinyl]-2-ethoxycarbonylimidazo[1,2-a]pyridine and 1-[3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl]-4-[2-(2-hydroxyethyl)imidazo[1,2-a]pyridin-5-yl]-2-piperazinecarboxamide, or a salt thereof or a prodrug thereof.

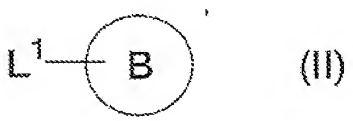
15. A pharmaceutical comprising the compound according to claims 1 or 2.

16. The pharmaceutical according to claim 15, which is an anticoagulant.

17. The pharmaceutical according to claim 15, which is an activated blood coagulation factor X inhibitor.

18. The pharmaceutical according to claim 15, which is a medicament for preventing or treating myocardial infarction, cerebral infarction, deep vein thrombosis, pulmonary thromboembolism, atherosclerotic obliterans, economy-class syndrome, or thromboembolism during and post operation.

19. A process for producing the compound according to claim 1, which comprises reacting a compound represented by the formula (II):



(II)

wherein L^1 represents a leaving group, and the other

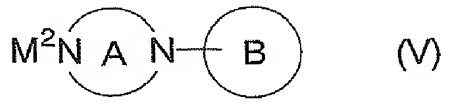
symbols have the same meanings as defined in claim 1, or a salt thereof, with a compound represented by the formula (III):

(III)

wherein M^1 represents a hydrogen atom, an alkali metal, an alkali earth metal or a leaving group, and the other symbols have the same meanings as defined in claim 1, or a salt thereof; or reacting a compound represented by the formula (IV):

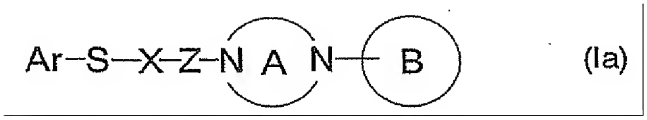
$Ar\text{-}S(O)a\text{-}X\text{-}Z\text{-}L^2$ (IV)

wherein L^2 represents a leaving group, and the other symbols have the same meanings as defined in claim 1, or a salt thereof, with a compound represented by the formula (V):



(V)

wherein M^2 represents a hydrogen atom, an alkali metal, an alkali earth metal or a leaving group, and the other symbols have the same meanings as defined in claim 1, or a salt thereof; or reacting a compound represented by the formula (Ia):



(Ia)

wherein symbols have the same meanings as defined in claim

1, or a salt thereof, with an oxidizing agent; or reacting a compound represented by the formula (VI):

$Ar\text{-}S(O)a\text{-}M^3$ (VI)

wherein M^3 represents a hydrogen atom, a hydroxyl group, an alkali metal, an alkali earth metal or a leaving group, and the other symbols have the same meanings as defined in claim 1, or a salt thereof, with a compound represented by the formula (VII):

(VII)

wherein X' represents an alkenyl group, an alkynyl group, or an alkyl group having a leaving group, and the other symbols have the same meanings as defined in claim 1, or a salt thereof; and optionally subjecting the compound obtained by the above reaction to hydrolysis, esterification, amidation, alkylation, acylation, reduction, oxidation or/and deprotection reaction.

20. 3-(5-Halogeno-2-indolyl)sulfonylpropionic acid, an ester thereof or an amide thereof, or 3-(1-tert-butoxycarbonyl-5-halogeno-2-indolyl)sulfonylpropionic acid, an ester thereof or an amide thereof, or a salt thereof.

21. A method for inhibiting blood coagulation in a mammal, which comprises administering an effective amount of the compound according to claim 1 or a salt thereof, or a prodrug thereof to the mammal.

22. A method for inhibiting an activated blood coagulation factor X in a mammal, which comprises administering an effective amount of the compound according to claim 1 or a salt thereof, or a prodrug thereof to the mammal.

23. A method for preventing or treating myocardial infarction, cerebral infarction, deep vein thrombosis, pulmonary thromboembolism, atherosclerotic obliterans, economy-class syndrome, or thromboembolism during and post operation in a mammal, which comprises administering an effective amount of the compound according to claim 1 or a salt thereof, or a prodrug thereof to the mammal.

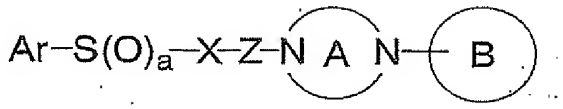
24. Use of the compound according to claim 1 or a salt thereof, or a prodrug thereof, for manufacturing a medicament for inhibiting blood coagulation.

25. Use of the compound according to claim 1 or a salt thereof, or a prodrug thereof, for manufacturing a medicament for inhibiting an activated blood coagulation factor X.

26. Use of the compound according to claim 1 or a salt thereof, or a prodrug thereof, for manufacturing a medicament for preventing or treating myocardial infarction, cerebral infarction, deep vein thrombosis, pulmonary thromboembolism, atherosclerotic obliterans, economy-class syndrome, or thromboembolism during and post operation.

ABSTRACT

An imidazopyridine derivative represented by the formula (I):



(I)

wherein Ar represents optionally substituted naphthyl, optionally substituted phenyl, optionally substituted indolyl, or optionally substituted benzothienyl; X represents an optionally substituted divalent hydrocarbon group; Z represents -CO-, -SO-, or $-SO_2-$; ring A represents an optionally substituted piperazine ring or optionally substituted homopiperazine ring; ring B represents an optionally substituted imidazopyridine ring; and a is 0, 1 or 2. It is useful as a therapeutic agent for thrombosis.